KU Leuven
Biomedical Sciences Group
Faculty of Medicine
Department of Public Health and Primary Care

DOCTORAL SCHOOL
BIOMEDICAL SCIENCES

EUTHANASIA AND ASSISTED SUICIDE FOR PSYCHIATRIC DISORDERS

CLINICAL AND ETHICAL PERSPECTIVES

Marie Elisabeth Nicolini

Jury:

Promotor:	Prof. Chris Gastmans (KU Leuven, Belgium)
Co-promotor:	Prof. Scott Y.H. Kim (National Institutes of Health, USA)
Chair examining committee:	Prof. Wim Janssens (KU Leuven, Belgium)
Chair public defense:	Prof. Pascal Borry (KU Leuven, Belgium)
Jury members:	Prof. Bernadette Dierckx de Casterlé (KU Leuven, Belgium)
	Prof. Koen Demyttenaere (KU Leuven, Belgium)
	Prof. Sigrid Sterckx (Ghent University, Belgium)
	Prof. Trudo Lemmens (University of Toronto, Canada)

Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences

May 2021

Table of Contents

Abstract

Background: The practice of euthanasia and assisted suicide for psychiatric disorders (psychiatric EAS) is only permitted in a few countries worldwide and remains a controversial issue. The practice has been legal since 2002 in Belgium and the Netherlands, but cases have started to increase mostly after 2011. The first empirical studies about this practice emerged after 2015 and most guidelines specific to psychiatric EAS, especially in Belgium, have been published only since 2017. Insights into the practice itself as well as the ethical debate surrounding the question are urgently needed.

Objectives: The overall objective of this project is to gain an in-depth understanding of the practice of psychiatric EAS, as well as of the ethical debate about the issue. This project aims at identifying the currently underexplored but salient clinical and ethical challenges with important policy and practical implications. It will contribute to informing the debate as well as to provide insights into how current guidance about the practice can be amended.

Methods: The relevant clinical and ethical challenges were identified and analyzed by: a) exploring the EAS evaluations of persons with personality-related disorders using mixed method approach; b) mapping the ethical debate about psychiatric EAS through a systematic review of reasons; c) providing empirical testing and ethical analysis of the most important and relevant arguments of the ethical debate.

Results: Psychiatric EAS evaluations of persons with personality-related disorders offer unique insights into two key requirements for EAS, namely unbearable suffering and irremediability. The systematic review of the ethical debate about the practice shows that arguments about these two requirements figure prominently in the debate. Furthermore, they are central in three important subdomains in the debate: 1) so-called “parity” (or non-discrimination) arguments, which focus on suffering, 2) what we mean by “irremediability” in psychiatry, and 3) the tension between psychiatric EAS and suicide prevention, with implications for how suffering and irremediability are conceived of in psychiatric EAS. Based on these results, a list of ten specific recommendations for future empirical and conceptual research is provided.

Conclusion: The practice of psychiatric EAS remains highly debated and controversial. This dissertation work points to some of the main clinical and ethical challenges associated with the practice, particularly as they relate to irremediability and unbearable suffering, and proposes ways to amend current guidance. Furthermore, it has mapped the international ethical debate about psychiatric EAS and outlined several suggestions for addressing its shortcomings. Finally, it has underscored the particular importance of the tension between psychiatric EAS and suicide prevention. This tension points to potentially inconsistent notions of informed consent in psychiatry, warranting further analysis.

List of abbreviations

In alphabetical order

DBT: Dialectical Behavior Therapy (type of psychotherapy)

DSM: Diagnostic and Statistical Manual of Mental Disorders

EAS: Euthanasia and/or Assisted Suicide

EAS physician: The physician who is in charge of providing EAS

ECT: Electroconvulsive therapy

GP: General Practitioner (primary care physician)

LEIF: Life End Information Forum (Belgium)

LST: Life-sustaining treatment

MAO-I: Monoamine Oxidase Inhibitor (type of antidepressant)

MBT: Mentalization-Based Treatment (type of psychotherapy)

NVVP: Dutch Psychiatric Association [*Nederlandse Vereniging voor Psychiatrie*]

PAD: Physician Aid-in-dying (synonym for EAS used in Chapter 4)

PPAD: Physician Aid-in-dying (synonym for psychiatric EAS used in Chapter 4)

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

Psychiatric EAS: EAS based primarily on a psychiatric condition

PTSD: Posttraumatic Stress Disorder

RTE: Regional Euthanasia Review Committee [*Regionale Toetsingscommissie Euthanasie*]

SCEN: Support and Consultation on Euthanasia in the Netherlands (SCEN) organization

SCEN consultant: Consultant trained by the SCEN (the Netherlands)

SFT: Schema-Focused Therapy (type of psychotherapy)

STAR*D Study: Sequenced Treatment Alternatives to Relieve Depression Study

TRD: Treatment-Resistant Depression

VVP: Flemish Psychiatric Association [*Vlaamse Vereniging voor Psychiatrie*]

Chapter 1: General Introduction

Background

Simona De Moor was an 85-year old Belgian woman who received euthanasia for 'reactive' depression. Her physician was the first to be referred to the Public Prosecutor in 2015 (De Standaard, 2015). Godelieve De Troyer was a 64-year old Belgian woman with depression who received euthanasia in 2012 and whose story came out in the New York Times in 2015 (Aviv, 2015). Her son filed a legal complaint with national courts, eventually taking the case to the European Court of Human Rights (Cheng, 2019). Aurelia Brouwers was a 29-year old Dutch woman with borderline personality disorder who died by euthanasia in 2018 (Pinedo, 2018). 'Emily' was a Belgian woman with a history of several suicide attempts who received euthanasia in 2018 at age 28, after she featured in an Economist documentary a few years earlier (TheEconomist, 2015). In June 2019, the death of Noa Pothoven, a Dutch 17-year old, created an international media controversy because it was initially misreported in English-language outlets as a case of euthanasia based on a psychiatric disorder (van Gelder and Bolwerk, 2019). While she did indeed ask for euthanasia, her request was refused; instead, her death was brought about by voluntary stopping eating and drinking, with the help of her family and doctors. The family members of Tine Nys, a 38-year old woman who died by euthanasia in 2010, initiated legal action. In January 2020, the Nys Criminal Court trial led to heated public discussions in Belgium about substantive and procedural criteria for euthanasia and assisted suicide when based on a psychiatric disorder (Cheng, 2019, Truyts, 2020).

The above-mentioned cases illustrate the highly contentious nature of the practice of euthanasia and assisted suicide when based primarily on a psychiatric disorder (psychiatric EAS), a practice permitted only in some European countries, such as Belgium, the Netherlands, Luxembourg and Switzerland (Griffith *et al.*, 2008, Jones *et al.*, 2017). The Chabot case ruling by the Dutch Supreme Court in 1994 led to the practice becoming effectively legal in 1997, even if the actual EAS laws in both the Netherlands and Belgium were enacted only five years later in 2002 (**Box 1.1**). Since 2010, the number of psychiatric EAS cases have grown slowly but steadily in Belgium and the Netherlands. In the Netherlands, they increased from 0.06% to 1.2% of all EAS cases during the period 2010–2017 (RTE, 2017). In Belgium, where cases of psychiatric disorder and dementia are reported together, the proportion rose from 0.5% of all cases reported in the period 2002–2007, increasing to 3.0% in the period between 2008-2013 (Dierickx *et al.*, 2017). While a few papers

were published early on after the legalization of the practice (Groenewoud *et al.*, 2004, Groenewoud *et al.*, 1997), empirical evidence focusing on psychiatric EAS started emerging mainly after 2015 (Bolt *et al.*, 2015, Dierickx *et al.*, 2017, Doernberg *et al.*, 2016, Kim *et al.*, 2016, Snijdewind *et al.*, 2015, Thienpont *et al.*, 2015, Verhofstadt *et al.*, 2017).

Clinicians in Belgium and the Netherlands remain divided when it comes to attitudes about the practice (Claes *et al.*, 2015, Haekens *et al.*, 2017, Onwuteaka-Philipsen *et al.*, 2017). Psychiatrists in the Netherlands appeared more ambivalent towards being involved in psychiatric EAS evaluations in 2015 than in 1995 (Onwuteaka-Philipsen *et al.*, 2017). A 2015 survey showed that only 34% of Dutch physicians support EAS based on a psychiatric disorder, compared to 85% in case of cancer and 82% in case of physical disease (Bolt *et al.*, 2015). Similarly, a Canadian survey with psychiatrists showed that only 29% supported psychiatric EAS, with 23.5% support in case of Axis-1 disorders (e.g. depression, schizophrenia) and only 9.3% support in case of Axis-2 disorders (i.e. personality disorders) (Rousseau *et al.*, 2017). Perhaps as a consequence of clinicians' ambivalence and need for concrete guidance, several guidelines have been published, most of which only after 2017 (Berghmans *et al.*, 2009, Brothers of Charity, 2017, Gastmans, 2018, NVVP, 2018, Orde der Artsen, 2019, Vandenberghe *et al.*, 2017, Verhofstadt *et al.*, 2019). In sum, discussions on the topic among the public, professionals and scholars have gained particular traction over the last couple of years and continue to do so.

In Canada, the Medical Assistance in Dying law enacted in 2016, limited to those whose natural death is "reasonably foreseeable", has led to discussions about extending access to the non-terminally ill (CCA, 2018, Kim and Lemmens, 2016). In 2020, Germany and Austria both lifted a ban on assisted suicide, ruling that the ban was unconstitutional and a violation of an individual's right to self-determination (Garg, 2020, Horn, 2020). In other countries permitting assisted suicide only in terminally ill patients, like some states in the United States and Australia, the question about whether or not access should be extended to psychiatric patients has entered the scholarly debate (Appelbaum, 2017, Hatherley, 2019, Kious and Battin, 2019).

Box 1.1. Psychiatric EAS: Background and Legal Criteria

Brief background

The practice of EAS has been legally permitted in the Netherlands for several decades prior to the Dutch EAS law, starting in the late seventies (Griffith *et al.*, 2008, Thomasma *et al.*, 1998). The practice of psychiatric EAS became effectively legal in the Netherlands, following the ruling of the Dutch Supreme Court on the Chabot case, named after the name of the psychiatrist Dr. Boudewijn Chabot. The physician assisted in the suicide of a 50-year old woman who wanted to die after having lost her two sons. She was not terminally ill and her suffering consisted of mental suffering. The Dutch Supreme Court ruled that assistance with suicide can be legally justifiable in the case of a patient whose suffering is not based on a somatic disorder and who is not terminally ill, i.e. that the "justification of necessity" for EAS applies equally in these cases. (For more detailed descriptions of the Chabot case and other court rulings leading to the legalization of psychiatric EAS in the Netherlands, see Griffith *et al*., 2008 and Thomasma *et al.*, 1998).

Note on the terms and concepts of euthanasia and assisted suicide

The Dutch EAS law allows for euthanasia and assisted suicide, even though in practice, a vast majority of persons die by euthanasia rather than by assisted suicide (RTE, 2018). Unlike the Dutch law, the Belgian law regulates only euthanasia (Adams and Nys, 2003, Nys, 2017). However, the Belgian Federal Control and Evaluation Commission on Euthanasia determined in their biannual evaluation report of 2004 that assisted suicide falls within the definition of euthanasia, and therefore falls under the Belgian euthanasia law, a decision which has been criticized as being beyond the purview of the Commission's competence (Nys, 2017). In this dissertation, the two terms ("euthanasia" and "assisted suicide") will be discussed together, using the commonly used abbreviation in the international literature on the topic ("EAS"). (For a more detailed comparison of the differences between the Belgian and Dutch laws, see Adams and Nys, 2003 and Nys, 2017).

Legal criteria according to the Belgian Act (Act Concerning Euthanasia of May 28, 2002)

The physician who performs euthanasia does not commit a criminal offense if she/he ensures that:

- The patient is an adult, emancipated minor, or a minor with capacity for discernment;
- The request is voluntary, well-considered and not the result of external pressure;
- The patient is in a medically hopeless condition experiencing constant and unbearable physical or psychological suffering that cannot be alleviated, resulting from a serious and incurable disorder caused by illness or accident.

In order to provide euthanasia, the physician must beforehand and in each case:

- Come to the conviction, together with the patient, that there is no reasonable alternative in his/her condition and that the request is voluntary;
- Ascertain the continued physical or mental suffering of the patient;
- Consult another physician about the serious and incurable nature of the disorder; the consulted physician must ascertain the constant, unbearable nature of the physical or mental suffering that cannot be alleviated; the physician consulted must be independent of the patient and of the attending physician.

If the death of the patient is not expected in the near future (i.e. if a patient is not terminally ill) the following additional requirements apply:

- a second physician, a psychiatrist or a specialist in the disorder in question, needs to be consulted;
- there has to be at least one month between the patient's written request and the performance of euthanasia.

(For more detailed information: see the Belgian Act, 2002)

Legal criteria according to the Dutch Act (Termination of Life on Request and Assisted Suicide Act of April 1, 2002)

In order for a patient to be eligible, the physician must:

- be satisfied that the patient's request is voluntary and well-considered;
- be satisfied that the patient's suffering is unbearable, with no prospect of improvement;
- have informed the patient about his situation and his prognosis;
- have come to the conclusion, together with the patient, that there is no reasonable alternative in the patient's situation;
- have consulted at least one other, independent physician, who must see the patient and give a written opinion on whether the due care criteria set out in (a) to (d) have been fulfilled;
- exercise due medical care and attention in terminating the patient's life or assisting in his suicide.

(For more detailed information: see the Dutch Act, 2002)

Other countries

Luxembourg

The Luxembourg Act on Euthanasia and Medically Assisted Suicide (2009) resembles the Dutch Act in that it applies to both euthanasia and assisted suicide. The legal criteria defined in the Luxembourg Act are roughly similar to those of the Dutch and Belgian Acts (Nys, 2017).

Switzerland

Switzerland does not have a specific EAS law but decriminalized assisted suicide (not euthanasia) in 1942. Assisted suicide is permitted if it is provided without selfish motive to a person with decision-making capacity (Hurst and Mauron, 2017). Hence, the conditions for assisted suicide are based on patient self-determination and are independent of the patient's proximity to death. While there is no unbearable suffering or irremediability requirement, the guidelines by the Swiss Academy of Medical Sciences do stipulate that these conditions be present (SAMS, 2018). Swiss cases of assisted suicide based on a mental disorder have been described (Black, 2012, Bruns *et al.*, 2016, Steck *et al.*, 2016).

Germany

In 2015, Germany enacted a law that criminalized "commercial promotion of assisted suicide". However, in February 2020, the German Constitutional Court overturned this ban, considering it to be unconstitutional (Horn, 2020). By grounding access to assisted suicide as a constitutionally protected liberty, without a requirement of a medical condition, the practice will de facto apply to both terminal and non-terminal illness cases. The exact scope of the right to self-determination that grounds access to assisted suicide, will likely continue to be subject to debate (Gather, 2020, Möller, 2020).

Austria

In December 2020, the Austrian Constitutional Court overturned a ban on assisted death, considering it a violation of an individual's right to self-determination. It deemed Section 78 of the Austrian Criminal Code which made act of "helping someone to commit suicide" a criminal offense, to be unconstitutional (Garg, 2020). As is the case in Germany, the ruling grants access to assisted suicide without requiring that the person be medically ill. The provision will come into effect in December 2021.

Canada

The Canadian Medical Assistance in Dying (MAID) law was enacted in 2016 and applies to persons whose natural death is 'reasonably foreseeable'. To receive MAID, a person must be capable of making health decisions, have a grievous and irremediable medical condition, have made a voluntary request that was not the result of extremal pressure. To meet the "grievous and irremediability medical condition" requirement, a person needs to meet the following: a) have a serious and incurable illness, disease or disability; b) be in an advance state of irreversible decline in capability, c) the illness, the disease or disability or that state of decline causes them enduring physical or psychological suffering that is intolerable to them and that cannot be relieved under conditions that they consider acceptable; d) their natural death has become reasonably foreseeable, taking into account all of their medical circumstances,

without a prognosis necessarily having been made as to the specific length of time that they have remaining. The Canadian law allows for MAID on the sole basis of a psychiatric disorder only if the person is deemed to have a 'reasonably foreseeable death' (CCA, 2018). Current Parliamentary discussions are ongoing, after a Quebec Superior Court stated the 'reasonably foreseeable death' requirement is unconstitutional (Rukavina, 2019). As of March 2021, Canada has an explicit commitment under its new law to legalize MAID when based on a sole mental disorder (with a sunset provision of 2 years) (Bryden, 2021).

Clinical, ethical and legal challenges

What trends are emerging from the practice?

From an empirical perspective, knowledge about the practice of psychiatric EAS, including clinical characteristics and patient-level socio-demographics, started to emerge mainly after 2015. Some of the main ethical issues relate to how the substantive criteria apply to mental disorders, in particular the requirements of a) a voluntary, well-considered request, b) unbearable suffering and c) irremediability (i.e. futility, or the lack of reasonable alternative treatment options).

Clinical and ethical issues relating to the voluntary, well-considered request requirement involved the assessment of decision-making capacity by clinicians, which only rarely involved formal capacity assessments (Doernberg *et al.*, 2016). In a first patient-level analysis of 66 Dutch cases, over half of the decision-making capacity assessments consisted of global clinical judgments. Decision-making capacity was often the cause of disagreements among consulted clinicians (Kim *et al.*, 2016). As for unbearable suffering, a Belgian qualitative study of 26 patient "testimonials" characterized unbearable suffering as relating to five domains: medical, intrapersonal (e.g. traumatic background history), interpersonal (e.g. serious conflicts with important others), societal (e.g. financial problems, unemployment) and existential factors (Verhofstadt *et al.*, 2017). Social isolation and loneliness were mentioned in over half the cases as contributing to the patients' suffering (Kim *et al.*, 2016). Finally, irremediability was the most common source of disagreement among consultants (Kim *et al.*, 2016), illustrating the contentious nature of this requirement. Although many patients had extensive treatment histories, over half had refused at least one type

of treatment and evidence-based treatments for depression, like monoamine oxidase inhibitors, were mentioned only in a minority of cases.

Besides insights about how the eligibility criteria apply in practice, the two main studies in Belgium and the Netherlands converged on the following two findings, warranting further research and analysis: a) a majority (70-77%) of persons who died by psychiatric EAS are women (as also illustrated anecdotally by publicized cases in the media) and b) the two most common psychiatric disorders are depression and personality disorders (Kim *et al.*, 2016, Thienpont *et al.*, 2015).

Should the practice be permitted?

From a theoretical-ethical perspective, discussions about whether the practice of psychiatric EAS is morally permissible have been ongoing for the past 25 years, since the Dutch 1994 Chabot case lead to the legalization of the practice in the Netherlands (Griffith *et al.*, 2008). While in Belgium and the Netherlands the practice has been legal since 2002, other countries are still debating its permissibility and its policy implications. Some of the main concerns related to permitting the practice have been that the legal criteria are broad and that greater uncertainty exists when applying these criteria to mental disorders (Appelbaum, 2017, Kim and Lemmens, 2016). For example, what "irremediability" exactly means and how it should be interpreted in psychiatric disorders is challenging, in part because chances of recovery are difficult to predict (Blikshavn *et al.*, 2017). Given that decision-making capacity, unbearable suffering and irremediability are either more difficult to assess, or only with greater degree of uncertainty, the risk of judgment error is greater in psychiatric EAS evaluations (den Hartogh, 2015, Kim, 2016a, Steinbock, 2017). In fact, a study of the Dutch cases where the due care criteria were considered as not met by the RTE, showed that a majority of cases where substantive requirements were not met involved non-terminally ill patients, including those with mental disorders (Miller and Kim, 2017).

Are there sufficient procedural safeguards?

The main procedural safeguards specific to psychiatric EAS include allowing for a waiting time between the request and the time of death and involving sufficient specific expertise. The Belgian law requires a waiting time of one month for all non-terminally ill patients, while the Dutch law

does not have such requirement (Griffith *et al.*, 2008, Jones *et al.*, 2017). Similarly, while the Belgian law requires a psychiatric consultation when a request is based on a mental disorder, the Dutch law does not. However, it is required by the Dutch Euthanasia Review Committees (EuthanasiaCode, 2018). But while laws and guidance require sufficient expert involvement, in practice there has been on ongoing difficulty in finding experts, including in the End-of-Life Clinics (founded in 2012 and since 2019 referred to as *Expertisecentrum Euthanasie*) (Huisman, 2017). This is particularly salient since most patients who receive EAS at the End-of-Life clinic are non-terminally ill (Levenseindekliniek, 2018, Snijdewind *et al.*, 2015).

Rationale

Gaining insight into the practice of psychiatric EAS as well as the ethical debate surrounding the question was both important and timely. The rationale for this project is outlined below.

First, investigating actual cases of persons who received psychiatric EAS was crucial, because it pointed to concrete clinical and ethical challenges associated with the practice. I decided to focus on mainly personality disorders because they appeared the most prevalent condition with depression among persons requesting psychiatric EAS, yet at the time little was known about what these requests looked like in practice. While depression, especially treatment-resistant depression, received some attention in the ethical literature on the topic (Miller, 2015, Steinbock, 2017), personality disorders had only been mentioned anecdotally in media reports (Pinedo, 2018). There was no systematized study of requests involving these patients. Psychiatric EAS evaluations of persons with personality disorders may be challenging to evaluate, in particular because chronic feelings of unbearable suffering and of a lack of future prospects, which are common among these patients, can overlap with the unbearable suffering and irremediability requirements (Swildens-Rozendaal and van Wersch, 2015). Furthermore, due to the complex interpersonal dynamics that personality disorders can evoke (NVVP, 2018), analyzing the requests of patients with these conditions can offer unique insights in the practice and its challenges. Finally, in my own clinical experience and practice, the topic of euthanasia came up primarily in persons with comorbid personality disorders, which prompted my interest in the topic. Hence, a focus on personality

disorders was both timely and clinically relevant, and could help elucidate and inform the conceptual discussion of the ethical issues at stake.

Second, the arguments in favor and against the practice itself, despite being at the center of heated public debates, had not been mapped in a systematic manner prior to this dissertation work. In the Netherlands and Belgium, the question of the legal permissibility of the practice was settled after the Chabot case ruling. However, the international debate did not truly become widespread until years after that one court ruling, when discussions on the topic gained more traction (Rooney *et al.*, 2018, Schuklenk and van de Vathorst, 2015). Hence, a systematic and comprehensive overview of the question was warranted, especially as more jurisdictions were legalizing EAS worldwide and some considered extending it to non-terminal, psychiatric disorders. This dissertation work coincided with Parliamentary discussions about extending EAS laws to non-terminal illness in Canada (starting in 2016) as well as in Germany (after 2015), so that this research could be timely and informative both for ongoing academic research as well as for health policy. Furthermore, it could provide insights and guidance for clinicians by mapping the different arguments in the debate.

Third, the main and widely used argument in public and academic debates, referred to as the parity or non-discrimination argument, had not been analyzed in detail. This argument essentially claims that if EAS is allowed for condition X, not extending access for condition Y amounts to the discrimination of patients with that condition Y. This idea is often taken for granted, without in-depth critical analysis of the argument. Analyzing the merits and limits of this argument would be crucial for further policy debates, particularly in countries considering broadening their EAS laws.

Fourth, within countries where the practice of psychiatric EAS is permitted, discussions about what irremediability means in psychiatry were ongoing. At the start of this dissertation work, the first Belgian guidelines had only just been published; consecutive guidelines adopting different interpretations of irremediability point to the fact that it is still the focus of debate. Therefore, an empirically-informed discussion of the ethical debate about irremediability was needed as a first step to inform clinical guidelines, but also policy debates about the acceptability of psychiatric EAS in countries where the practice was not yet permitted.

Fifth, a consistent finding in previous studies on the practice was the preponderance of women among psychiatric EAS cases, ranging between 70-77% of cases. This needed further analysis, particularly since it appeared to relate to an important conceptual issue, namely the tension between psychiatric EAS and suicide prevention. An analysis of this gender gap was crucial for further research on this tension, as well as to elucidate some of the reasons why this gap exists in the first place and what potential venues for further research might be in this area.

In sum, this dissertation work combines empirical and normative methods to clarify and analyze some of the pressing clinical-ethical challenges associated with the practice of psychiatric EAS. It focuses on empirical evidence as a starting point for ethical discussion throughout the project. A clear understanding of the concrete complexities associated with the practice is essential, especially given the contentious nature of this topic. Ethical discussion needs to be empirically-informed, to avoid cross-talk and philosophical argumentation that is based on idealized scenarios only. This can in turn lead to sound argumentation that informs policy-making.

Objectives

The general objective of this dissertation work is to gain an in-depth understanding of the practice of psychiatric EAS and of the ethical debates surrounding this issue. This project aims at identifying the underexplored but relevant clinical and ethical challenges, as well as the larger policy questions related to the practice. The specific objectives of this project are the following:

(a) To gain insight into the practice of psychiatric EAS and physicians' decision-making;
(b) To characterize the ethical debate around psychiatric EAS;
(c) To analyze the structure and limits of the parity or non-discrimination argument;
(d) To characterize the role of irremediability and prognosis prediction in the ethical debate;
(e) To examine the tension between psychiatric EAS and suicide prevention;
(f) To formulate specific recommendations for the debate and practice of psychiatric EAS.

Outline and Methodology

Outline

As mentioned above, the goal of this project is to outline important and concrete clinical and ethical challenges that the practice of psychiatric EAS poses, for clinicians as well as for policy-makers. To achieve this goal, I will divide this thesis into three main parts, consisting of five chapters. The aim of the first part is to elucidate some of the highly complex challenges associated with psychiatric EAS requests from persons with personality disorders. The second part aims at mapping the ethical debate about psychiatric EAS in a systematized and comprehensive manner. The results of these first two parts will inform the main ethical questions related to the practice and be crucial in determining the priority axis (i.e. relevant subdomains) for further analysis, as laid out in the third part.

The three main parts of this project are the following:

a) Clinical and ethical challenges in the practice of psychiatric EAS (Chapter 2)
b) Mapping the ethical debate about psychiatric EAS (Chapter 3)
c) Ethical analysis of three subdomains relevant to policy-making (Chapters 4-6)

An overview of the content of each chapter of this dissertation can be found below:

1. Chapter (1) General introduction to the dissertation.

2. Chapter (2) provides an in-depth analysis of psychiatric EAS evaluations in the Netherlands, with a focus on personality-related disorders.

3. Chapter (3) maps the reasons for and against the practice of psychiatric EAS found in the literature; my aim is to characterize the ethical debate and identify its gaps.

4. Chapter (4) provides a detailed ethical analysis of the non-discrimination argument that is central in ethical discussions about the practice, identifying its merits and shortcomings.

5. Chapter (5) analyzes the empirical premises of arguments regarding irremediability found in the ethical debate, and provides normative guidance for further ethical discussion.

6. Chapter (6) analyzes the gender gap in psychiatric EAS and how it informs the tension between psychiatric EAS and suicide prevention.

7. Chapter (7) General Discussion, in which I describe the following:1) Summary of the general findings of Chapters 2-6, 2) Specific recommendations for the debate about and the practice of psychiatric EAS, 3) Potential limitations and methodological considerations of this project, 4) Avenues for further research, and 5) Conclusion.

Methodology

The methodology used throughout this thesis involves a combination of empirical and normative analysis. The empirical component includes a combination of qualitative and quantitative methods. The normative component involves a conceptual and analytical appraisal of ethical arguments. A more detailed description of the methods used per study is described below.

Chapter 2 consists of an *empirical mixed-method analysis* of individual case reports published by the Dutch Euthanasia Review Committees, made available online to ensure transparency and accountability. They are, to date, the only patient-level case reports available among all countries where psychiatric EAS – or EAS more broadly – is permitted. Selection of the cases was made based on pre-established inclusion criteria, which were broadly construed as to capture all cases of persons with personality-related disorders. The cases were analyzed by two independent reviewers using a directed content analysis, as described previously (Hsieh and Shannon, 2005, Kim *et al.*, 2016). The coding scheme used for the analysis was developed iteratively in light of the main research domains. Finally, the quantitative part consisted of frequencies, tabulations, and exploratory post-hoc tests of bivariate associations, consistent with the descriptive goals of the study.

Chapter 3 describes a systematic review of reasons, a *normative review* of the literature with an empirical (qualitative and quantitative) component (Sofaer and Strech, 2012, Strech and Sofaer, 2012). It is a systematic review in that it reports a transparent and reproducible search strategy across several electronic databases and uses the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for article selection (Liberati *et al.*, 2009, Moher *et al.*, 2009). In the empirical (qualitative and quantitative) component of the review, the reasons are identified and extracted through qualitative content analysis, and then reported in a quantitative manner. The qualitative part of reason extraction is both deductive and inductive: it includes the use of a pre-established coding scheme based on the known arguments for and against the practice (deductive part), which is amended iteratively during the analysis (inductive part). The final and major part of the process is the grouping of reasons into themes -or content domains- and within each theme, per area of disagreement or normative engagement. This part of the process consists of an evaluation of the normative arguments, allowing for a clear overview of each content domain and their respective areas of ethical disagreement.

Chapters 4-6 combine results of the first two parts to establish the domains of interest for further empirically-informed *ethical analysis*. In particular, key results of Chapter 2 relating to unbearable suffering, irremediability and the gender gap among psychiatric EAS cases, will guide the choice of domains identified in Chapter 3: a) the non-discrimination argument, which is based on suffering, b) irremediability and c) how the gender gap informs the tension between psychiatric EAS and suicide prevention. The method for each chapter is briefly outlined below.

Chapter 4 uses the method of close analysis, an established method in analytic philosophy, of one major type of argument in the debate (i.e. the non-discrimination argument). This process includes several steps: a) searching for suppressed or implicit premises, b) reconstructing the argument and c) analyzing the truth of each premise. Based on this analysis, one can conclude whether the argument in question is valid (i.e. the conclusion follows from the premises) and/or sound (i.e. the argument is valid and all premises are true).

Chapter 5 provides an evidence-based review of the empirical assumptions underlying the main arguments in the debate about irremediability. The review consists of a separate and reproducible

search in PubMed based on 3 research questions derived from the main areas of disagreement in the ethical debate. The aim is to further inform the ethical debate in a way that is supported by the current state-of-the-art knowledge about conceptualizations of irremediability in psychiatry.

Chapter 6 describes an ethical analysis that is informed by the contemporary suicide literature and theories. It clarifies what the tension is about from an empirical standpoint and how the high prevalence of women informs that tension (empirical component), before laying out the policy implications of this analysis (ethical component).

Chapter 2: Euthanasia and Assisted Suicide of Persons with Psychiatric Disorders: The Challenge of Personality Disorders

Nicolini M., Peteet J., Donovan G., Kim S. (2020). Euthanasia and Assisted Suicide of Persons with Psychiatric Disorders: The Challenge of Personality Disorders. *Psychological Medicine* 50(4), 575–582. https://doi.org/10.1017/S0033291719000333

Abstract

Background: Euthanasia or assisted suicide (EAS) for psychiatric disorders, legal in some countries, remains controversial. Personality disorders are common in psychiatric EAS. They often cause a sense of irremediable suffering and engender complex patient–clinician interactions, both of which could complicate EAS evaluations.

Methods: We conducted a directed-content analysis of all psychiatric EAS cases involving personality and related disorders published by the Dutch regional euthanasia review commit- tees (N = 74, from 2011 to October 2017).

Results: Most patients were women (76%, n = 52), often with long, complex clinical histories: 62% had physical comorbidities, 97% had at least one, and 70% had two or more psychiatric comorbidities. They often had a history of suicide attempts (47%), self-harming behavior (27%), and trauma (36%). In 46%, a previous EAS request had been refused. Past psychiatric treatments varied: e.g. hospitalization and psychotherapy were not tried in 27% and 28%, respectively. In 50%, the physician managing their EAS were new to them, a third (36%) did not have a treating psychiatrist at the time of EAS request, and most physicians performing EAS were non-psychiatrists (70%) relying on cross-sectional psychiatric evaluations focusing on EAS eligibility, not treatment. Physicians evaluating such patients appear to be especially emotionally affected compared with when personality disorders are not present.

Conclusions: The EAS evaluation of persons with personality disorders may be challenging and emotionally complex for their evaluators who are often non-psychiatrists. These factors could influence the interpretation of EAS requirements of irremediability, raising issues that merit further discussion and research.

Introduction

Euthanasia or assisted suicide (EAS) for psychiatric disorders, legal in some European countries such as Belgium and the Netherlands, remains controversial (**Box 2.1**). Although psychiatric EAS cases comprise a relatively small number of cases overall, their proportion has increased from 0.06% to 1.2% during the period 2010 to 2017 in the Netherlands (RTE, 2017). Personality disorders are present in at least half of those who request and receive psychiatric EAS (Kim *et al.*, 2016, Thienpont *et al.*, 2015). Given their chronicity, prevalence, significant symptom burden, and impact on outcomes of co-morbid Axis I psychiatric disorders (Tyrer *et al.*, 2015), it is perhaps not surprising that these disorders are so common in patients requesting EAS. Such disorders raise some important issues for further examination. In particular, the characteristic features of personality disorders, such as feelings of helplessness, hopelessness, and suicidal thoughts (which are usually addressed therapeutically) may be difficult to distinguish from feelings of intolerable and hopeless suffering (which are eligibility criteria for EAS) (Swildens-Rozendaal and van Wersch, 2015). Thus, it may be challenging to evaluate whether there really is no prospect of improvement and no alternative to EAS in such cases. Furthermore, because personality disorders are known to evoke complex interpersonal interactions, including with health care providers (Berghmans *et al.*, 2009), managing such dynamics in the EAS evaluation process may require special care and expertise.

The debate regarding psychiatric EAS has mainly focused on treatment-resistant depression as the paradigm case (Blikshavn *et al.*, 2017, Schuklenk and van de Vathorst, 2015, Steinbock, 2017), and personality disorders have received little attention so far despite their prevalence and their unique challenges in the context of psychiatric EAS. This study aimed to describe the characteristics of patients with personality disorders who receive EAS and how their requests for EAS are evaluated, given the potential challenges in evaluating these patients' beliefs about irremediability of their condition.

Methods

According to the RTE website (**See Box 2.1**) as of October 1, 2017, a total number of 232 psychiatric EAS cases had been reported to the RTE since 2010: 2 cases in 2010, 13 cases in 2011,

14 cases in 2012, 42 cases in 2013, 41 cases in 2014, 56 cases in 2015, 60 cases in 2016 and 4 cases in 2017[1]. 116 of these 232 cases (50%) were published and available on the RTE website during the period between June 1, 2015 and October 1, 2017.

We selected 74 cases based on the goals of our study, using the following criteria. Category 1 included the cases where a formal diagnosis of a personality disorder was reported (n=48; 65%), including personality disorder not otherwise specified (NOS). Because the RTE reports are not always written with precise clinical language and because persons can have clinically significant symptoms of a personality disorder without fully meeting diagnostic criteria (Oldham, 2006, Zimmerman *et al.,* 2012), we included two more categories of patients. Category 2 included the cases without a formal diagnosis but with explicit mention of prominent personality difficulties or "traits" (n=16; 22%). This included specific mention of cluster A, B or C "personality traits"[2], or "impaired personality development". Because of the clinically significant overlap between (cluster B) personality disorders and interpersonal hardship following trauma as seen in some disorders, e.g. complex PTSD (Giourou *et al.,* 2018), a third category included cases with explicit mention of early traumatic events and chronic residual symptoms of interpersonal dysfunction (n=10; 13%), defined by the presence of chronic/complex PTSD (n=6), self-harming behavior (n=8), psychotic or dissociative symptoms (n=4) or a combination of those.

We analyzed the cases using a directed content analysis, as described previously (Kim *et al.*, 2016). Cases were read and coded independently by a bioethicist-psychiatrist (M.N) and a consultation-psychiatrist (J.P.). The first author (M.N.) is a native Dutch speaker and reviewed all of the cases in original Dutch. For the second author (J.P.), of the 74 cases, 40 cases had been translated into English and have been analyzed for a different set of variables, as described previously (Kim *et al.*, 2016). The remaining 34 cases were machine translated (using Google translate). Discrepancies in coding occurred in 9% of coded items (505/5476 total) and for each discrepancy, the Dutch-speaking author reviewed the accuracy of the English translation by comparing it with

[1]The number for 2017 reflects a partial count due to our cutoff date for purposes of our analysis. In 2018, the RTE reported the final number of reported psychiatric EAS as 83 for 2017. Six case descriptions from 2011 are no longer available on the RTE website, illustrating that the RTE website is a dynamic entity. These cases are available from the authors upon request. [2] See Appendix 2A for a description of the different personality disorder clusters.

the original Dutch text. Discrepancies involving a difference in judgment between the two readers were revolved through discussion, involving an additional reader, a bioethicist-psychiatrist (S.K.).

The coding scheme was developed iteratively and in light of the main research domains: a) patient characteristics; b) patients' treatment histories; c) treating physicians' responses to EAS requests; d) the EAS evaluation process (duration, consultants involved, relevant texts regarding due care criteria, and RTE judgements) e) emerging themes, such as features of the End-of-Life Clinic cases. The data were analyzed using SPSS statistical data package, version 25. Analysis consisted of frequencies and tabulations, and exploratory post hoc tests of bivariate associations, without hypothesis testing given the descriptive goals of the study.

Results

Characteristics of patients

Seventy-six percent (n=56) of patients were women (**Table 2.1**). 19% were younger than 40 and 51% were older than 60. About two-thirds of the cases (65%, n=48) mentioned cluster B personality disorders or traits, and 18% (n=13) were personality disorders not otherwise specified. In the remainder, 9% (n=7) had cluster C traits only and 3% (n=2) mentioned cluster A traits.

All but two patients had comorbid Axis I psychiatric conditions (97%, 72 cases) (**Table 2.2**). The three most common conditions were depression (unipolar or bipolar) in 70% (n=52), posttraumatic stress disorder or prominent post-traumatic symptoms in 31% (n=23) and anxiety disorders in 31%. Somatoform disorders were present in 19% of the cases (n=14) (including conversion, somatization and unspecified somatoform disorders).

38% (n=28) had only psychiatric diagnoses and 62% (n=46) had in addition one or more physical comorbidities. These conditions included musculoskeletal and rheumatologic disorders in 23 cases (including osteoarthritis, osteoporosis, polyarthritis, bone fractures), chronic or generalized pain disorders (chronic fatigue, fibromyalgia, chronic pain) in 8 cases, neurological disorders (migraine, anosmia, stroke and sequels, ataxia, head trauma, neurogenic bladder and quadriplegia) in 14 cases, cardiovascular disease (heart failure, cardiac surgery and myocardial infarct) in 3 cases, and pulmonary disease (mostly COPD) in 5 cases.

Forty-two percent of the patients were described as functionally dependent (n=31). This was the case in 11% (3 out of 28) of the cases with only psychiatric problems, and in 61% (28 out of 46) of the cases with physical comorbidity.

Treatment history

Seventy-three percent (n=54) of patients had a psychiatric admission in the past, and in 14% (n=10) some form of compulsory or other court-ordered treatment was mentioned (**Table 2.3**). Psychotherapy had been tried in 72% (n=53), mostly of unspecified nature (39 of 53). Among the known standard evidence-based treatments for cluster B personality disorders, ranging from cognitive-behavioral to psychodynamic treatments (Cristea *et al.*, 2017, Zanarini, 2009), dialectical behavior therapy (DBT) was not mentioned in any cases, mentalization-based treatment (MBT) was considered but not tried in one case, and schema-focused treatment (SFT) was mentioned once.

About a third (34%, n=25) of patients received electroconvulsive therapy (ECT) at some point; treatment with all indicated medication types for depression including a monoamine oxidase inhibitor (MAO-I) was mentioned in 7% (n=5). A subspecialist involvement in the patient's treatment history was mentioned in 15% (n=11) of the cases (for example, when patients were referred to a "specialized clinic" or "tertiary academic center"). However, a subspecialist involvement in the EAS evaluation process itself occurred only in one case [2013-27], where a psychiatrist who specialized in geriatric psychiatry evaluated an elderly patient.

In one of the two cases without an Axis-I diagnosis [2015-19], there was no mention of any form of psychiatric treatment.

About one half (51%, n=38) of the patients refused some form of treatment which included hospital admissions, medications, psychotherapy, other modalities (including ECT) or a combination. 43% (16 of 38) of these patients refused more than one treatment modality. The main reason for refusals was a lack of motivation (61%, 23 of 38).

In a fourth (26%) of the cases (n=19), physicians appeared to consider a treatment option and then determined that it need not be tried. The most common reasons given were that the physician thought the patient may not benefit from it (n=13) or was not motivated enough (n=6). For example: "In theory there were other treatment options for the personality disorder [..] but the

psychiatrist noted it was an open question whether the patient could cope with these treatments and whether she could form and uphold an adequate treatment relationship" [case 2016-01]. As in this case, in more than half of the cases where a physician considered and then dismissed a treatment option (10 out of 19 cases), there was also a mention of the patients not wanting treatment. In most cases, the patients expressed their refusal first.

Refusal of prior EAS requests

Overall, 46% (34 of 74) of EAS cases occurred after at least one doctor refused to provide it. In 29 (39%) cases, the treating GP refused to endorse the EAS request. The main reason for refusal was a non-specific "for own reasons" or "complexity" of the case. The GPs mostly explained complexity either as the combination of physical and psychiatric conditions ["the GP was very involved but found it difficult to perform EAS in this particular case, whereby somatic and psychic suffering were entangled" (2014-40)] or in reference to the patient's personality ["the complexity… was grounded in the fact that the patient was a difficult, not very nice man who had difficulties expressing himself" (2014-37)].

In 32 (43%) cases the request was made to a treating psychiatrist, and half (n=16) of the psychiatrists refused to perform EAS. The main reasons were "own reasons" (n=11), due criteria considered not met (n=3) and reasons of conscience (n=2).

In 11 cases (15%), both the patient's treating psychiatrist and the GP refused the request. Notably, most (8 of 11) of these were recent cases (2015-2017), meaning that 30% (8 of 27) of published cases from those years involved both the GP and the psychiatrist refusing the request. All 11 cases received EAS at the End-of-Life Clinic, and in 9 of those cases the EAS physician was not a psychiatrist.

Roles of psychiatrists and other doctors in the EAS evaluation process

In over a third (36%, 27 of 74) of cases, there was no mention of current treating psychiatrist involvement at the time of the EAS request (**Table 2.4**). In 30% (22 of 74) of the cases, the EAS physician was a psychiatrist. In 50% of all cases, the EAS physician was new to the patient (n=37), and most of those patients received EAS at the End-of-Life Clinic (n=32).

Although the Dutch law does not require that the EAS consultant be a psychiatrist even in psychiatric EAS cases, the RTE's Code of Practice of 2015 requires consulting an independent psychiatrist (Swildens-Rozendaal and van Wersch, 2015). In 41% of the cases a psychiatrist was one of the official EAS consultants (n=30); in 53% (n=39) of cases the EAS physician relied on a less formal "second opinion" of a psychiatrist; and in 5 cases (7%) there was no independent psychiatrist involved. In those 5 cases, the RTE found that the due care criteria were not met in one case (2014-01), did not address the lack of psychiatric consultation (2012-62 and 2014-74), or explained its discretion in applying the rules (2011-124658 and 2015-45).

End-of-Life Clinic and patients with physical comorbidities

Forty-three percent of the cases were referred to the End-of-Life Clinic (n=32), either after refusal of a physician (n=26) or through self-referral (n=6) but not all cases of physician refusals ended up at the End-of-Life Clinic. End-of-Life Clinic cases were more likely to be older than 60 [75% (24 of 32) vs. 33% (14 of 42), p=0.0005, Fisher's exact test]. Although not statistically significant, a current treating psychiatrist was less often involved [53% (17 of 32) vs. 71% (30 of 42) in End-of-Life Clinic cases, p=0.14]. The patients were less likely to have tried psychotherapy [53% (17 of 32) vs. 86% (36 of 42), p=0.004] and the physician evaluating/performing EAS was less often a psychiatrist [13% (4 of 32) vs. 43% (18 of 42), p= 0.005]. The official consultant was a psychiatrist in 38% (12 of 32) but 13% (2 of 16) in 2015-2017; a second opinion psychiatrist was involved in 72% (23 of 32).

Patients with physical comorbidity were more likely to have had a prior EAS request refused by their psychiatrist, referred to the End-of-Life Clinic, and less likely to have tried psychotherapy (**Table 2.5**).

Assessment of the unbearableness of suffering

According to the RTE (following the Dutch Psychiatric Association Guidelines), the unbearableness of suffering, while defined subjectively by the patient's perspective, "must be palpable ["invoelbaar"] to the physician" (Swildens-Rozendaal and van Wersch, 2015). Among the 116 psychiatric EAS cases published by the RTE, the term "invoelbaar" is used in 34 cases and 31 of those (91%) were cases with personality disorders or difficulties: e.g., "the

unbearableness of the suffering was palpable for the physician by the way the patient looked, the way she spoke about her life, the sadness and powerlessness that she emanated" (2011-125900).

Discussion

Despite having received little attention so far, persons with personality disorders constitute more than half of those who request and receive psychiatric EAS (Kim *et al.*, 2016, Thienpont *et al.*, 2015). Addressing such EAS requests from persons with personality disorders could be particularly challenging as these patients may have self-destructive behavior, a traumatic background, feelings of helplessness, hopelessness and despair (Verhofstadt *et al.*, 2017) which may create challenges in EAS evaluation of irremediability. Furthermore, personality difficulties can influence interpersonal dynamics that could affect the EAS evaluation process.

Characteristics of patients

Most patients had a long history of a complex set of comorbid conditions. In contrast to a Belgian report of 100 requestors of psychiatric EAS who were younger with few medical co-morbidities (Thienpont *et al.*, 2015), we found that 51% were over 60 years old, nearly two-thirds had comorbid physical disorders and 61% were functionally dependent to some degree. Almost all had co-morbid Axis-I psychiatric disorders (with 70% having 2 or more). In only 2 patients were personality difficulties the sole psychiatric basis for EAS (both had comorbid chronic pain). Thus, EAS of persons with personality difficulties most often occurs in persons with long psychiatric and medical histories. Many treating physicians were aware of these issues as indicated by frequent references to "complexity" of cases when explaining their refusal of EAS requests.

On the other hand, these patients shared features common to suicidal persons with personality difficulties. Women, who are more likely to attempt suicide (Bernal *et al.*, 2007, O'Connor *et al.*, 2018), were disproportionately represented (76%). Many patients had a depressive disorder (70%), a previous suicide attempt (47%, with multiple attempts in 36%), self-harm (27%) and a traumatic background (36%). There was evidence of demoralization and difficulties relating to others: "She suffered from the meaninglessness of her existence […] Because she was not able to connect with others, she experienced deep despair and loneliness" (2015-32: 50-60y, personality disorder NOS

and chronic pain) and "[t]he patient's suffering consisted of continuous negative thoughts and negative judgments about herself" (2014-78: 30-40y, PTSD, borderline personality disorder, multiple suicide attempts).

Evaluation of EAS requests

Irremediability is a key due care requirement; patients need not to go through "every conceivable form of treatment" but they do not meet the requirement if they refuse "a reasonable alternative" (Swildens-Rozendaal and van Wersch, 2015). Not all patients appeared to receive some standard treatments, such as ECT and MAO-inhibitors for mood disorders. Over a fourth of patients (27%) had not been hospitalized. Most notably, psychotherapy, the primary treatment for personality disorders (Bateman and Fonagy, 2015, Bateman *et al.*, 2015), was not tried in 28%.

It is known that having a personality disorder is a predictor of poor outcome of comorbid axis-I disorders (Newton-Howes *et al.*, 2014, Tyrer *et al.*, 2015). However, both cognitive and psychodynamic psychotherapeutic treatments have proven to be effective for personality disorders (Bateman and Fonagy, 2009, Cristea *et al.*, 2017, Leichsenring and Leibing, 2003, McMain *et al.*, 2009, Swenson and Choi-Kain, 2015). For example, dialectical behavior therapy (DBT) and mentalization based treatment (MBT) have shown to reduce suicidal behavior in patients with borderline personality disorders (Bateman and Fonagy, 2009, Kvarstein *et al.*, 2018, Linehan *et al.*, 2006, Linehan *et al.*, 1994) and MBT and schema-focused treatment (SFT) to reduce depressive symptoms in these patients (Bamelis *et al.*, 2014, Bateman and Fonagy, 2009). In fact, treatment guidelines of both the American Psychiatric Association and the Netherlands Institute of Mental Health and Addiction (Trimbos Institute) advise DBT, MBT or SFT for the treatment of persons with borderline personality disorders (Oldham *et al.*, 2010, Trimbos, 2008), and applying evidence-based treatments for personality disorders is cost-effective (Meuldijk *et al.*, 2017). However, DBT was not mentioned in any of our case reports, MBT was mentioned but not tried in one case, and SFT occurred once. What factors, then, may explain the variability of past psychiatric treatments, psychotherapeutic in particular, in patients with personality disorders receiving psychiatric EAS?

One reason for these results may be that due to the patients' chronic, complex histories, clinicians were inclined to accept the patients' perspectives more readily. This would be consistent with a trend that Dutch psychiatrists note as an evolution towards accepting patients' subjective definition of irremediability (den Hartogh, 2017, Onwuteaka-Philipsen *et al.*, 2017). Second, the high prevalence of medical comorbidities in persons with psychiatric disorders may lead physicians to treat the patients predominantly as "medical" patients. This might be influenced by clinicians' general tendency to consider personality disorders as coincidental rather than as a true diagnosis (Tyrer *et al.*, 2015, Van and Kool, 2018). It is notable that over a third (36%) did not have a treating psychiatrist at the time of their EAS request, only 30% of the EAS physicians were psychiatrists, and half of the EAS evaluations were managed by physicians new to the patient. When other psychiatrists were involved, this tended to be for cross-sectional evaluation of EAS eligibility, not treatment.

A third reason may be that counter-transference issues [*(tegen)overdracht*] may no longer be emphasized. Although counter-transference has long been recognized as a challenge in EAS evaluations involving personality disorders (Berghmans *et al.*, 2009, Groenewoud *et al.*, 2004), the term is not mentioned in any of our case reports. Yet vigilance regarding counter-transference seems especially important given that the RTE directs physicians to use their own reactions to patients' suffering ["palpable" ("*invoelbaar*")] in EAS evaluations. It is notable that "palpable" is used almost exclusively (91%) in cases with personality difficulties. Thus, physicians seem uniquely emotionally affected by the suffering of patients with personality disorders seeking EAS. This raises the question of whether the RTE's guidance may lead physicians to operate within a patient's psychopathology. For example, a clinician may identify with a patient's perception of irremediability (e.g. "nothing will work"): "Other therapeutic avenues were explored including Mentalization Based Therapy (MBT). However, the patient did not want to be treated anymore. The physician agreed with her as her personality structure was deemed not strong enough to endure such a drastic treatment (MBT) without her suicidal tendencies or depression getting out of control" (2014-78). However, as mentioned earlier, this evidence-based treatment is especially beneficial for high clinical severity patients (Kvarstein *et al.*, 2018), with positive effects on suicidality and depressive symptoms (Bateman and Fonagy, 2009).

Implications

The results of our study raise questions about how to interpret the irremediability requirement in patients with personality disorders. There is substantial evidence for the effectiveness of several psychotherapeutic treatment options on outcome measures such as depressive symptoms or suicidal behavior (Bateman and Fonagy, 2009, Cristea *et al.*, 2017, McMain *et al.*, 2009). Furthermore, although the number of studies are limited (Leichsenring and Leibing, 2003), long-term follow-up shows that the majority of persons with personality disorders achieve sustained remission (Zanarini *et al.*, 2012). Whether these results would be generalizable to some of the more complex cases in our study -with multiple psychiatric and somatic comorbidities- is an open question. However, it is important to note that treatment studies targeting personality disorders and psychiatric comorbidity such as depression are still lacking (Van and Kool, 2018). Similarly, the complex interplay between psychiatric and somatic comorbidity, in particular in female patients, needs further study (WHO, 2001).

The results of this study may support recent proposals to improve psychiatric EAS evaluation that include a longer-term evaluation, more than one independent expert input, and a parallel therapeutic focus on recovery while the EAS request is evaluated (Gastmans, 2018, Vandenberghe *et al.*, 2017). Our results show that young, physically healthy psychiatric patients with personality disorders may be more likely to receive expert attention attuned to their personality disorders. But in older patients with multiple somatic conditions, this may be less so. These results suggest that these patients with both psychiatric and somatic conditions may require a higher level of psychiatric expertise during the evaluation process given the complexity of their clinical conditions and their sparser past psychiatric treatment history. In these patients' assessments, a "medical model" seems to predominate rather than a more psychologically oriented model focusing on coping and interpersonal skills. While the Dutch euthanasia law allows for physicians' discretion, the results raise the question of whether sufficient safeguards are in place, including the necessary expertise in personality disorders.

Involvement of experts may be limited by the reluctance of psychiatrists to be involved in EAS (Onwuteaka-Philipsen *et al.*, 2017) and the physician-centric nature of EAS evaluations (with no official role for other mental health professionals, such as psychologists and other therapists, who

may have more expertise in the long-term management of personality issues). The need for more expertise in personality disorders may also apply to the RTEs given its difficulties in finding mental health professionals to serve on the RTE (Doernberg *et al.*, 2016, Kurniawan and van der Zwaard, 2018).

Finally, these results, which are based on retrospective reviews, suggest a need to prospectively investigate psychiatric EAS in persons with personality disorders, focusing on the patients' perceptions underlying their requests for EAS and on their clinicians' decision-making when evaluating those requests, with special attention to how the granted EAS requests differ from those that are denied.

Limitations

There are several limitations to our study. First, the RTE does not publish all psychiatric EAS cases, limiting generalizability of studies based on only the published cases. These were all completed EAS cases, and do not include requests that did not lead to EAS. However, the RTEs intend the published cases to serve educational, precedent setting functions so that they do carry a special significance (RTE, 2014). Further, these published reports comprise the only source of reliable EAS case information beyond anecdotal media reports. Second, the qualitative coding requires judgment in interpretation. Moreover, given that the reports are not always written in clinical language, there was often a lack of specificity regarding the type of personality disorder and their diagnostic descriptions. Although two-thirds of our cases had a formal diagnosis of a personality disorder, we chose to risk over inclusion in order to include all patients with personality difficulties. Third, our use of statistical tests was post-hoc, using a small sample. However, this report comprises all available case descriptions of an infrequent but growing phenomenon which allowed for patient-level analysis. Finally, because this article focuses mainly on the irremediability requirement, we did not address the issue of mental capacity in personality disorders, a complex issue (Ayre *et al.*, 2017, Owen *et al.*, 2008) which requires a separate discussion.

Conclusion

Personality disorders are common in persons receiving psychiatric EAS. For most patients, their personality difficulties were part of complex clinical histories with multiple psychiatric and physical comorbidities. These patients generally had long histories of suffering, with features common to suicidal persons with personality disorders, including histories of serious self-harm, suicide attempts, and demoralization. However, in the EAS evaluations of these patients, especially if the patients were older with physical co-morbidities, the EAS physicians tended to be non-psychiatrists who were new to them at a specialty EAS clinic and relied on less formal, cross-sectional psychiatric second opinions. The current practice of psychiatric EAS involving persons with personality difficulties raises important questions about whether the special challenges associated with personality disorders are being thoroughly addressed. The lack of specialist and longitudinal evaluations may impede an objective evaluation of irremediability and limit the focus on recovery. The issues raised are worthy of further investigation and discussion, especially as some jurisdictions consider legalization of psychiatric EAS.

Box 2.1.

The Termination of Life on Request and Assisted Suicide Act was enacted in 2002, formalizing what had been legally protected practice based on court decisions (Griffith *et al.*, 2008). The Act's due care criteria for EAS require that the physician must be satisfied that patient's request be voluntary and well-considered and the patient's suffering is unbearable and with no prospect of improvement. The physician must inform the patient about his/her situation and prognosis and must come to the conclusion, together with the patient, that there is no reasonable alternative in the patient's situation. The procedural criteria require that at least one, independent physician be consulted and that due medical care is exercised in performing EAS (Swildens-Rozendaal and van Wersch, 2015).

All cases must be reported to the Dutch regional euthanasia review committees (*Regionale Toetsingscommissies Euthanasie* [RTE]; https://www.euthanasiecommissie.nl/uitspraken-en-uitleg) which reviews all EAS reports. There are 5 RTEs, with the goal of providing uniform guidance. They are committed to transparency and publish on their website a selection of case reports that are deemed "important for the development of standards" to provide "transparency and auditability" of EAS practice (RTE, 2014, Swildens-Rozendaal and van Wersch, 2015). Given the controversial nature of psychiatric EAS, the RTE has published a relatively high proportion of the cases - publishing all psychiatric cases from 2013 for example (RTE, 2014). The RTE has since reduced the number of published psychiatric EAS cases.

The End-of-Life Clinic (*Levenseindekliniek*) is an organization founded in 2012, which provides EAS evaluation for persons whose treating physician declined to perform EAS. Most patients who receive EAS at the End-of-Life Clinic are non-terminally ill (Levenseindekliniek, 2018). A review of the activity of the End-of-Life Clinic has been published (Snijdewind *et al.*, 2015) .

Table 2.1. Characteristics of 74 patients who received EAS for personality and related disorders	**No.**	**%**
Women	56	76
Age group (years)*		
- 18-30	3	4
- 30-40	11	15
- 40-50	9	12
- 50-60	13	18
- 60-70	21	28
- 70-80	11	15
- 80-90	6	8
History of a suicide attempt	35	47
History of multiple suicide attempts	27	36
History of self-harm	20	27
History of early childhood maltreatment	27	36
History of dissociative symptoms	10	14
Functional status involving some degree of dependence	31	42
Institutionalization specifically mentioned	15	20
Social isolation or loneliness mentioned	42	57

*Age groups overlap but reflect the categories used in the RTE reports.

Table 2.2. Psychiatric axis-I comorbidity	**No.**	**% (*)**
Number of comorbid conditions		
4	6	8
3	18	24
2	29	39
1	19	26
0	2	3
Type of comorbid conditions		
Depression and bipolar disorder	52	70
PTSD or posttraumatic residua	23	31
Anxiety disorders	23	31
Somatoform disorders	14	19
Eating disorders	11	15
Psychotic disorders	8	11
Substance abuse	7	9
Neurocognitive	6	8
Other, including autism, complicated bereavement, dissociative disorder, alexithymia	9	12

(*) This column does not add up to 100% because some patients had multiple diagnoses.

Table 2.3. Treatment history	**No.**	**(%)**
Psychiatric admissions in past	54	73
Compulsory treatment in past	10	14
Psychotherapy tried	53	72
Subtype (one or combination)		
- (Cognitive) behavioral therapy	10	14
- EMDR	4	5
- STEPSS[#]	3	4
- Other	39	53
ECT	25	34
Depression protocol including MAO-I	5	7
Subspecialist involved at any point of treatment	11	15
Physician dismisses treatment option	19	26
Refusal of treatment by patient	38	51
Basis of refusal by patient[*]		
- Lack of motivation	23	61
- Doubts about efficacy	6	16
- Side effects or risks	11	29

*Total sum more than 100 because some patients refused for different reasons

[#]In the Dutch reports, the term “VERS” was used (abbreviation for *Vaardigheidstraining Emotie Regulatie Stoornis)*, a supportive group treatment similar to STEPPS (“Systems training for emotional predictability and problem solving”) (Van Wel *et al.*, 2009)

Table 2.4. Process of EAS evaluation	**No.**	**%**
Current treating psychiatrist involved	47	64
EAS Physician is new to patient	37	50
EAS Physician is a psychiatrist	22	30
Psychiatrist one of the official EAS consultants	30	40
Psychiatrists consulted during EAS evaluation		
- Both second opinion psychiatrist and EAS psychiatrist consultant	15	20
- Second opinion psychiatrist only	39	53
- EAS psychiatrist consultant only	15	20
- No psychiatrist consulted	5	7
Disagreement among consultants	15	20
Basis for disagreement		
- Irremediability	9	12
- Voluntary and well-considered request	6	8
- Unbearable suffering	3	4
- Other	1	1
Discussion of capacity status: any discussion beyond statement that patient had capacity[#]	20	27
Time of evaluation 1st official consultant		
- <1 week (prior to EAS)	9	12
- <1 month	39	53
- >1 month	26	35
Time of evaluation by second opinion psychiatrist		
No second opinion psychiatrist	20	27
Time not specified	4	5
< 1 week (prior to EAS)	2	3
<1 month	10	14
>1month	38	51

[#]Any discussion beyond the statement that the patient made a “well-considered request.”

Table 2.5. Comparison of psychiatric EAS evaluation of patients with and without physical comorbidity	**With physical comorbidity**	**Without physical comorbidity**	**p#**
Prior psychiatric admission	67% (31 of 46)	82% (23 of 28)	.19
Prior psychotherapy	63% (29 of 46)	86% (24 of 28)	.06
Treating psychiatrist at time of EAS request	57% (26 of 46)	75% (21 of 28)	.14
Prior EAS refusal by psychiatrist*	68% (13 of 19)	23% (3 of 13)	.03
Referral to End-of-Life Clinic	54% (25 of 46)	25% (7 of 28)	.02

Fisher's exact test; *Among those who had a prior treating psychiatrist, n=32.

Appendix 2A. Personality Disorders: Clusters, Types and Main Features[#]		
Cluster A	**Cluster B**	**Cluster C**
Paranoid personality disorder Distrust and is suspicious of others Unjustified doubts about trustworthiness of others Reluctant to confide in others Hostile reaction to perceived slights Tendency to bear grudges **Schizoid personality disorder** Lack of desire of close relationships Preference for solitary activities Limited range of emotional expression Indifference to the praise or criticism of others **Schizotypal personality disorder** Ideas of reference Odd beliefs or magical thinking Unusual perceptual experiences Odd thinking and speech Suspiciousness Inappropriate or constricted affect Odd, eccentric or peculiar behavior Lack of close friends Excessive social anxiety	**Borderline personality disorder** Efforts to avoid real or imagined abandonment Unstable and intense interpersonal relationships Identity disturbance Recurrent suicidal behavior, impulsivity Affective instability Chronic feelings of emptiness Intense, difficulty controlling anger Transient, stress-related paranoid ideation or severe dissociative symptoms **Histrionic personality disorder** Uncomfortable when not the center of attention Inappropriate sexually seductive or provocative behavior Rapidly shifting expression of emotions Use of physical appearance to draw attention Impressionistic speech style Self-dramatization, exaggerated expression of emotions Easily influenced by others Considering relationships more intimate than they are **Narcissistic personality disorder** Need for admiration Lack of empathy for others Grandiose sense of self-importance Fantasies about power and success Arrogant attitude or sense of entitlement Interpersonally exploitative	**Avoidant personality disorder** Extreme shyness Feelings of inadequacy Sensitivity to criticism Fear of disapproval or embarrassment Reluctance to take personal risks **Dependent personality disorder** Need for others to assume responsibilities Difficulties expressing disagreement with others Difficulties making decisions without reassurance from others Uncomfortable feeling or helplessness when alone Lack of self-confidence **Obsessive-compulsive personality disorder** Preoccupation with orderliness, perfection and control Perfectionism interfering with task completion Excessive devotion to work and productivity Excessive conscientiousness, scrupulosity and inflexibility in morality and values Rigidity and stubbornness *This is not the same as obsessive compulsive disorder*

	Antisocial personality disorder Failure to conform to social norms with respect to lawful behaviors, irresponsibility Deceitfulness, impulsivity, irritability Disregard for safety of self or others Lack of remorse	

[#]Adapted from the Diagnostic and Statistical Manual 5 (DSM 5). The table contains a non-exhaustive list of some key features of the different personality disorder types. The DSM 5 defines a personality disorder as "an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment. The pattern is manifested in two (or more) of the following areas: cognition, affectivity, interpersonal functioning and impulse control."
(Reference: https://dsm.psychiatryonline.org/doi/10.1176/appi.books.9780890425596.dsm18)

Appendix 2B. Three case descriptions[#]

Case 2014-78: A woman in her 30s with post-traumatic stress disorder, borderline personality disorder and recurrent depressive episodes, had endured several voluntary and involuntary hospitalizations related to multiple suicide attempts. She underwent "various forms of drug treatments and electroconvulsive therapy, all with mediocre results". The patient's suffering consisted of very low self-esteem, "continuous negative thoughts and negative judgments about herself" and omnipresent "thoughts that she was not worthy to live, could not handle life, and wanted to die". She "experienced nightmares and relived her childhood traumas". A year before her death, after she had made a euthanasia request to her previous therapist, the EAS physician[1] (psychiatrist) took over the treatment with regard to the euthanasia process. A second opinion psychiatrist was consulted, and concluded that the patient was mentally competent. Other therapeutic options were discussed, including mentalization based therapy (MBT), but the patient refused further treatment. The physician "agreed with her as her personality structure was deemed not strong enough to endure such a drastic treatment (MBT) without her suicidal tendencies or depression getting out of control". The physician then consulted an independent (primary care) SCEN-consultant[2], who visited the patient twice within a month prior to her death. The consultant found that the alternatives mentioned were no longer realistic and concluded that due care criteria were met.

Case 2014-82: A woman in her 50s with serious psychiatric pathology for the past 35 years (post-traumatic stress disorder, dissociative disorder, borderline or multiple personality disorder, and extended periods of depression and psychosis), had been hospitalized many times for suicide attempts. She also had chronic migraines and chronic neurological pain after back surgery. She had been treated extensively with psychotropic medication, including opiates and weekly intramuscular antipsychotics. The many drug and psychotherapeutic treatments did not help. The patient's suffering consisted of "continuous intrusions, extreme dissociative symptoms in which 'alters' emerged, compulsive behavior, obsessive thoughts, chronic anxiety, loneliness and conflicts with her relatives". The patient made a euthanasia request to her treating primary care physician and psychiatrist, both of whom could not honor her request. The patient then registered at the End-of-Life Clinic, four months prior to death, where the EAS physician (non-psychiatrist), asked for a second opinion psychiatrist. The psychiatrist advised other pharmacotherapies and electroconvulsive therapy, but these were not tried. The EAS physician then consulted two independent psychiatrists. The first found the patient competent and advised to consult a second psychiatrist. The second psychiatrist stated that "the focus was on psychotherapeutic treatment, which the patient had had exhaustively", concluding that there was no reasonable alternative. The first psychiatric consultant then visited the patient again, five days prior to death, and concluded, based on his two visits, that due care criteria had been met.

Case 2016-78: A man in his 30s with chronic and increasing schizoaffective disorder, personality disorder (mixed cluster B and C) and prominent obsessive-compulsive traits, had had almost the entire protocol for the treatment of schizoaffective depression. He had been "hospitalized multiple types, had tried many types of medication and undergone ECT". Despite being treated by a psychiatrist and a FACT[3] team, this did not reduce the patient's suffering, which consisted of "an empty feeling in his head" and "not being able to think". The patient, who had been an intelligent, sociable man and suffered from his loss of abilities, described "a feeling of painful emptiness and intense pain in the soul, which he couldn't bear and which was overwhelming". The patient had talked about euthanasia previously

with his treating physicians, who were not willing to endorse his request. The patient requested euthanasia to the EAS physician (non-psychiatrist) 3.5 months prior to death. This physician consulted an independent psychiatrist, who found that there were remaining pharmacological and psychotherapeutic options. The EAS physician "acknowledged that these were possible in theory, but that with the patient's lack of motivation these couldn't be forced on the patient" and that "psychotherapeutic treatments would have little chance of success because of the patient's low coping capacity". The EAS physician then consulted an independent SCEN-consultant (non-psychiatrist), who visited the patient two weeks prior to death, and concluded that due care criteria were met.

[#]The full case reports can be found on the following link: https://www.euthanasiecommissie.nl/uitspraken-en-uitleg. We have summarized three cases that illustrate some of the key themes from the report. These have been added in response to an anonymous reviewer's suggestion and for the purpose of illustration only. Therefore, these 3 cases cannot be considered a representative sample of the 74 cases included in our study.

Abbreviations:
[1] EAS physician: The physician who was in charge of providing EAS
[2] SCEN: Consultants trained by the Support and Consultation on Euthanasia in the Netherlands (SCEN) organization
[3] FACT: Flexible Assertive Community Treatment

Chapter 3: A Systematic Review of Reasons For and Against Euthanasia and Assisted Suicide for Psychiatric Disorders

Nicolini M.E., Kim S.Y.H., Churchill M.E., Gastmans C. (2020). Should Euthanasia and Assisted Suicide for Psychiatric Disorders be Permitted? A Systematic Review of Reasons. *Psychological Medicine* 50(8), 1241-1256. https://doi.org/10.1017/S0033291720001543

Abstract

Background: Euthanasia and assisted suicide based on a psychiatric disorder (psychiatric EAS) continue to pose ethical and policy challenges, even in countries where the practice has been allowed for years. We conducted a systematic review of reasons, a specific type of review for bioethical questions designed to inform rational policy-making. Our aims were twofold: (1) to systematically identify all published reasons for and against the practice (2) to identify current gaps in the debate and areas for future research.

Methods: Following the PRISMA guidelines, we performed a search across seven electronic databases to include publications focusing on psychiatric EAS and providing ethical reasons. Reasons were grouped into domains by qualitative content analysis.

Results: We included 42 articles, most of which were written after 2013. Articles in favor and against were evenly distributed. Articles in favor were mostly full-length pieces written by non-clinicians, with articles against mostly reactive, commentary-type pieces written by clinicians. Reasons were categorized into eight domains: (1) mental and physical illness and suffering (2) decisional capacity (3) irremediability (4) goals of medicine and psychiatry (5) consequences for mental health care (6) psychiatric EAS and suicide (7) self-determination and authenticity (8) psychiatric EAS and refusal of life-sustaining treatment. Parity- (or discrimination-) based reasons were dominant across domains, mostly argued for by non- clinicians, while policy reasons were mostly pointed to by clinicians.

Conclusions: The ethical debate about psychiatric EAS is relatively young, with prominent reasons of parity. More direct engagement is needed to address ethical and policy considerations.

Introduction

Euthanasia or assisted suicide (EAS) primarily on the basis of psychiatric disorders (psychiatric EAS) is permitted in some European countries such as the Netherlands and Belgium (**Table 3.1**). In these countries, the number of cases has been slowly but steadily increasing since 2010 and empirical papers on the topic have rapidly increased since 2015 (De Hert *et al.*, 2015, Dierickx *et al.*, 2017, Doernberg *et al.*, 2016, Kim *et al.*, 2016, Miller and Kim, 2017, Nicolini *et al.*, 2020b, RTE, 2017, Thienpont *et al.*, 2015, van Veen *et al.*, 2019, Verhofstadt *et al.*, 2017). In Canada, the 2016 medical assistance in dying law, limited to those whose natural death is "reasonably foreseeable", engendered an ongoing controversy about whether access should be extended to the non-terminally ill (CCA, 2018). A recent Quebec court ruling declared the proximity to death requirement unconstitutional, raising important implications for psychiatric EAS in the country (Rukavina, 2019).

But even in the European countries where psychiatric EAS has been legal for years, the practice remains controversial (Griffith *et al.*, 2008, Jones *et al.*, 2017, RTE, 2018) and some cases have led to court cases (Cheng, 2019, Day, 2018). Attitudes among professionals vary: a 2016 Dutch survey indicated that 37% of psychiatrists found it conceivable to provide psychiatric EAS, compared to 47% in 1995 (Onwuteaka-Philipsen *et al.*, 2017). Similarly, Belgian mental health professionals have been divided over the issue (Bazan, 2015, Claes *et al.*, 2015, Haekens *et al.*, 2017). Perhaps as a consequence of this, various guidelines by major healthcare institutions and professional organizations have been written and revised, especially over the last few years to guide and regulate the practice (EuthanasiaCode, 2018, NVVP, 2018, Orde der Artsen, 2019, Vandenberghe *et al.*, 2017, Verhofstadt *et al.*, 2019).

Although the landmark Chabot case in the Netherlands occurred over 25 years ago (Griffith *et al.*, 2008), a systematic review of the literature on the ethical reasons for and against the practice is lacking. Systematic reviews of ethics literature are intended to inform bioethics argumentation, but also policy-making (McCullough *et al.*, 2007, Sofaer and Strech, 2012, Strech and Sofaer, 2012). We performed a systematic review of reasons, a specific type of review for bioethical questions which identifies and extracts all published reasons for or against a contested policy or

practice. Its purpose is to provide a comprehensive and systematic descriptive overview of the ethical debate rather than a philosophical evaluation of the reasons (McDougall, 2014, Mertz *et al.*, 2017, Strech and Sofaer, 2012). The aims of our review were twofold: First, to identify what reasons have been provided for why psychiatric EAS should or should not be permitted as a practice or by law. Second, to describe and characterize notable trends in the debate and identify current gaps and areas for future research.

Methods

Search strategy

We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (Liberati *et al.*, 2009, Moher *et al.*, 2009) (**Fig 3.1**). One author (M.N.) searched, from inception until Nov 6th, 2018, the following databases: PubMed/MEDLINE, Web of Science (Core Collection), PsycInfo, Philosopher's Index, Embase, Scopus, and CINAHL. A search strategy comprised of keywords from three groups was used: mental illness; euthanasia and assisted suicide; and ethics and philosophy. The full search strategy (**Appendix 3A**) was reviewed and validated by an independent librarian from the National Institutes of Health. The search was updated to June 12th, 2019. Finally, we used the snowball method and our own experience to add publications not detected in the seven databases. EndNote X9 was used to manage and screen citations.

Inclusion and exclusion criteria

We included a publication if:

I. It focused on psychiatric EAS defined as EAS in which mental illness is the primary reason for the request.
II. Its primary aim was to provide ethical reasons why psychiatric EAS should or should not be permitted (as a practice or by law).
III. The publication was peer-reviewed.
IV. The publication was written in English, Dutch, Italian or French.

Condition (I) excluded papers focusing on EAS in: persons with neurodegenerative diseases (e.g. dementia); terminally ill persons with a psychiatric disorder, where the primary reason for requesting EAS was the physical condition and not the psychiatric disorder and persons without medical conditions (e.g. "tired of living" or "completed life" cases). It also excluded papers about the ethics of suicide rather than assisted death and "euthanasia" of the mentally ill in the context of historic eugenic practices.

Condition (II) excluded empirical studies, purely descriptive clinical or legal—rather than normative— case analyses, and articles mainly providing an overview of the reasons for or against psychiatric EAS rather than defending one's own position. Articles in which the overall position taken was less clear but where the authors directly responded to others' positions were included because responding to an argument implies taking a position. Finally, we included case discussions only if they contained ethical arguments, principles or recommendations. Condition (III) excluded non-peer reviewed articles, newsletters, guidelines and textbook chapters. We included letters, commentaries and editorials only if they were peer-reviewed. When it was not clear from the journal's website whether a publication was peer-reviewed, we contacted their editorial office.

Study selection and data extraction

Two readers (M.N.; M.C.) independently performed the title/abstract screening following the predefined inclusion and exclusion criteria. Full-text screening and data extraction were independently performed by two readers for English articles (M.N.; M.C.) and non-English articles (M.N.; C.G.). Discrepancies were resolved through discussion involving an additional reader (S.K.). We identified and extracted reasons using the following steps. First, we identified reasons for and against psychiatric EAS. Second, we included a passage as a reason for or against psychiatric EAS if the author proposed the reason directly as an argument for or against, or if the context made it clear that it fell within their overall argument. If the authors discussed an idea but not clearly as a reason for or against, we did not include it. Third, we grouped the reasons into content domains by qualitative content analysis. This was done by multiple readings, highlighting the meaningful units (passages of reasons), labeling them (codes), and grouping them into content

domains using a combined deductive and inductive method (Elo and Kyngas, 2008, Graneheim and Lundman, 2004, Mertz *et al.*, 2017).

Results

The systematic search yielded 2,553 articles (**Fig. 3.1**). Of those, 35 were eligible for inclusion. We identified 6 additional eligible articles pursuing reference lists and included one article from the updated literature search, for a total of 42 articles.

Publication characteristics

The dates of publication ranged from 1998 to 2019, but 81% (34/42) were published in 2013-2019. Articles were published in the following fields: medicine (52%), bioethics (40%), law (5%) and social work (2%). Based on the corresponding author's credentials, half of the articles were written by authors with a clinical background (e.g. psychiatry, palliative care, geriatrics, social work). Virtually all clinicians were physicians (95%, 20/21), mostly psychiatrists. The other half were written by authors with a background other than medical (e.g., philosophy, bioethics, law). When an author had both clinical and non-clinical credentials, they were counted as clinicians. Overall, most (71%, 30/42) articles were written by authors in a country where EAS of some type has been legalized (in the country or in some jurisdictions within it). Over half (52%) were from a country where the eligibility for EAS is tied to its proximity to natural death (**Appendix 3B**). 90% of articles (38/42) were written in English, 4 were written in Dutch or French.

The articles were nearly evenly distributed with regards to their overall position (48% articles in favor and 52% against). The authors' position was determined by their conclusions and whether the majority of arguments given were in favor or against psychiatric EAS. For example, some authors presented mostly arguments against or in favor of psychiatric EAS, even though they also expressed reasons for the other side—in which case we classified them according to their predominant position (den Hartogh, 2015, Steinbock, 2017, Vandenberghe, 2018, Vink, 2012). The position taken varied depending on the corresponding author's background and the article type. Most articles in favor of psychiatric EAS were full-length articles written by non-clinicians (75%, 15/20). Publications against psychiatric EAS tended to be shorter, commentary-type pieces written by clinicians (73%, 16/22).

Reasons for and against psychiatric EAS

We identified 107 reasons (62 pro, 45 con) which were mentioned 407 times (232 pro, 175 con mentions) (**Figure 3.2**). We categorized reasons into 8 content domains as shown in Table 2, using the following labels and listed in descending order of frequency: 1) mental and physical (illness and suffering) 2) decisional capacity 3) irremediability 4) goals of medicine and psychiatry 5) consequences for mental health care 6) psychiatric EAS and suicide 7) self-determination and authenticity 8) psychiatric EAS and refusal of life-sustaining treatment (LST) (**Table 3.2**). Within each domain, we described the reasons according to the specific topic of disagreement they related to. 9% of mentions (36 of 407) directly responded to another paper included in this review; this direct engagement between authors started only in 2013.

Mental and physical illness or suffering

Within this domain (65 pro and 32 con mentions), two main areas of discussion emerged: parity (non-discrimination) between mental and physical illness or suffering (59 mentions) and policy concerns (38 mentions). Parity reasons, mostly raised by non-clinicians, stated that if EAS is permitted in persons with terminal, physical illness, differential treatment in persons with mental illness is not justified, based on the parity of mental illness and suffering with physical illness and suffering. Assertions of parity between mental and physical *suffering* (24 mentions) were the most frequently cited parity reasons in favor of psychiatric EAS, followed by reasons of parity between mental and physical *illness* (20 mentions). Responses against parity which focused on differences between mental and physical *illness*, such as the often poorly understood etiology of mental illnesses, were raised by clinicians only. Non-clinicians arguing against parity instead pointed to the fact that there are morally relevant differences that could justify differential treatment in EAS between mental and physical illness. Only one author argued against the parity of mental and physical *suffering*, that the intolerability of suffering may be a symptom of the disorder.

Policy considerations largely focused on the issue of ‘false positives’ (the ending of lives in persons who in fact do not meet the criteria). Some authors, from different backgrounds, focused on the increased risk of error (i.e. diagnostic or prognostic) in psychiatric disorders and the

unfeasibility of implementing rigorous safeguards. Others, mostly non-clinicians in favor of psychiatric EAS, noted that the risk of false positives is not sufficient to justify prohibiting psychiatric EAS or that the risks could be adequately addressed by implementing rigorous safeguards.

Decisional capacity

The domain of decisional capacity figured prominently in the debate (38 pro and 31 con mentions). In the major disagreement (17 pro and 16 con mentions), those arguing for psychiatric EAS, mostly non-clinicians, emphasized that some persons with mental disorders seeking psychiatric EAS are decisionally capable (e.g., arguing that not permitting psychiatric EAS would amount to presuming incompetence). Others argued that the main issue is the difficulty of reliably determining capacity and the need for extra caution. A second point of contention (14 and 11 mentions) regarded evaluations of decisional capacity in psychiatric EAS requests. Authors in favor, largely non-clinicians, stated that capacity evaluations for psychiatric EAS should not be different than any other capacity evaluation in health care. Others, both clinicians and non-clinicians, argued against this and focused on the impact a psychiatric disorder might have on specific abilities for capacity (i.e., on the ability to appreciate how a decision applies to oneself). A third theme (7 pro and 3 con mentions) focused specifically on the threshold for capacity assessment. Some non-clinicians argued it should be independent of the stakes, or should be low in order to err on side of self-determination. Other authors argued that the threshold should be high to minimize false positives. Finally, one reason against the practice, with no corresponding reason in favor, related to voluntariness (i.e. that undue external pressure can influence a person's choice).

Irremediability

The irremediability domain (33 pro and 36 con mentions) contained reasons relating to the irremediability of mental disorders. However, authors sometimes used the term to also mean irremediability of mental suffering. The main area of disagreement (12 pro and 27 con mentions) related to whether truly irremediable cases exist in psychiatry and whether they can be reliably identified. The most common reason in favor was the view that mental illness or suffering can be truly irremediable. Responses, raised by authors from different backgrounds, pointed to practical

challenges in reliably determining irremediability, such as difficulties in predicting prognosis or the lack of a unified interpretation of "treatment-refractory". Only few, non-clinicians, responded that we can reliably interpret irremediability, e.g., with the help of statistical tools. In the second dispute (11 pro and 7 con mentions), some authors in favor, mostly non-clinicians, argued that judgments about irremediability should not merely depend on statistical chances of recovery but instead on the person's own judgment. Others responded that determinations of irremediability should be made by both patient and clinician. Within this dispute, reasons in favor partially overlap with (and respond to) some reasons against the practice raised in the domain of decisional capacity, namely that a mental disorder can influence the cognitive aspects of a patient's judgment about her chances of recovery. The third subdomain (6 pro and 2 con mentions) involved the question of whether waiting for possible new treatments, such as ketamine for treatment-resistant depression, is or is not justified.

Goals of medicine and psychiatry

This fourth domain (25 pro and 26 con mentions) contained reasons focusing on the impact of psychiatric EAS on medical and psychiatric practice. The main dispute (13 pro and 14 con mentions) was whether permitting psychiatric EAS would positively or negatively affect the patient-physician relationship. Reasons against were largely raised by clinicians, responded to by authors from different backgrounds. The second dispute (12 pro and 12 con mentions) was whether psychiatric EAS is compatible with the goals of medicine and psychiatry, involving even engagement from authors from different backgrounds. Authors in favor argued that it can be compatible with physicians' role (e.g. consistent with professional integrity and physician's role as gatekeepers of lethal drugs) and duty to relieve suffering. Authors responded that the two are incompatible (e.g. pointing to professional integrity, the social meaning of medicine or the duty to preserve life) and that there is a normative difference between a right to treatment and a right to psychiatric EAS.

Consequences for mental health care

In the fifth domain (17 pro and 20 con mentions), potential consequences of allowing psychiatric EAS for mental health care more broadly were raised. The first point of contention (7 pro and 12

con mentions) was about the effect of psychiatric EAS on mental health care policy. Clinicians argued that it may negatively impact mental health care and that other factors need to be addressed first. Authors from different backgrounds responded that the two are not mutually exclusive. The second disagreement (10 pro and 8 con mentions) concerned the potential consequences for vulnerable populations. All authors arguing that consequences could be negative were clinicians. Authors in favor responded with empirical reasons (e.g., that there is little evidence for this concern) or normative ones (e.g., that expansion of EAS to other populations is not necessarily a bad outcome).

Psychiatric EAS and suicide

This domain focused on the tension between psychiatric EAS and suicide prevention policies (17 pro and 18 con mentions). Within the main disagreement (12 pro and 14 con mentions), authors in favor, mainly non-clinicians, argued that psychiatric EAS can prevent suicides and that denying access to psychiatric EAS forces persons to commit suicide. Others, from mixed backgrounds, pointed to the conflict with the duty to prevent suicide and argued that there is no duty to provide, nor a corresponding right to receive, psychiatric EAS. The second disagreement (5 pro and 4 con mentions), largely argued for by non-clinicians, related to whether patients' eligibility should or should not depend on their physical ability to end their lives.

Self-determination and authenticity

Reasons about self-determination and authenticity (22 pro and 6 con mentions) were, like decisional capacity, closely related to the general concept of autonomy. However, we categorized them separately as they addressed concerns distinct from decisional capacity. Reasons in this domain were raised by authors from different backgrounds. Most reasons related to self-determination (18 pro and 4 con mentions) and whether persons with a psychiatric disorder can have a rational wish to die or make their own free choices. Some responded that respect for autonomy is not sufficient grounds for psychiatric EAS. A second disagreement (4 pro and 2 con mentions) related to authenticity and the impact of psychiatric disorders on the ability to live up to one's goals and values.

Psychiatric EAS and refusal of life-sustaining treatment

Within this last domain (15 pro and 6 con mentions), the main disagreement related to the relationship between EAS and refusing LST. Some non-clinicians in favor of psychiatric EAS argued that that there is no morally relevant distinction between refusing LST and psychiatric EAS. Authors against psychiatric EAS, from different backgrounds, instead claimed that the justifications for respecting a person's refusal of LST do not provide justifications for psychiatric EAS.

Discussion

Rational and informed policy making about psychiatric EAS requires a systematic understanding of the reasons for and against the practice. We conducted a systematic review of reasons, a special form of review for bioethical questions, for this purpose. Its secondary aim was to describe and characterize notable trends in the debate and identify current gaps and areas for future research.

Main findings of reasons for and against the practice

The policy implications of parity reasons were disputed by both clinicians and non-clinicians. Some authors in favor, mostly non-clinicians, argued that parity requires extending EAS laws to include persons with mental illness as a matter of principle. Hence, the possibility of false positives should be tolerated to reduce overall suffering (Cholbi, 2013, Provencher-Renaud *et al.*, 2019, Reel, 2018, Rooney *et al.*, 2018, Sagan, 2015, Schuklenk and van de Vathorst, 2015, Tanner, 2018). Other authors in favor of the practice instead raised policy concerns (Steinbock, 2017, Vandenberghe, 2018). These authors raised similar concerns about whether decisional capacity and irremediability can be reliably identified.

Other disagreements were not parity-based. Some depended on empirical assumptions which will need further testing, such as the dispute about prognosis prediction in psychiatry. For example, machine learning methods to predict prognosis at the individual level are being developed (Chekroud *et al.*, 2016, Dinga *et al.*, 2018) and may further inform the psychiatric EAS debate. Other empirical questions include the effects of psychiatric EAS on mental health care and the

patient-physician relationship. Although there is some literature on the potential problem of (counter-)transference in the context of EAS and psychiatric EAS in particular (Berghmans *et al.*, 2009, Groenewoud *et al.*, 2004, Hamilton *et al.*, 1998, Jones *et al.*, 2017), other effects on the patient-physician relationship are unknown.

Some normative disputes resulted from different underlying premises or philosophical assumptions. For example, whether irremediability should be defined by 'objective' clinical judgment based on prevailing evidence or by the requestor's own, 'subjective' judgment is not an empirical question. Thus, it appears disputes about irremediability trace back to larger conceptual disputes. Notably, no author explicitly argued that autonomy is a sufficient condition for permitting psychiatric EAS. Similarly, the normative question of what *threshold* should be used in evaluating decisional capacity will partly depend on how one weighs the relief of suffering against the unwarranted ending of an incapacitated patient's life. Some have pointed to this tension (den Hartogh, 2015) or argued explicitly that the relief of suffering should prevail regardless of decisional capacity (Varelius, 2016b).

Finally, whether psychiatric EAS is compatible with the duty to prevent suicide partly depends on whether one relies on a view that challenges, or instead relies on, current ways of conceptualizing suicide prevention. For example, current practices allow involuntary commitment to prevent suicide. Furthermore, while some argued that psychiatric EAS could prevent suicides, the underlying debated question of whether psychiatric EAS should be considered a form of suicide or not (CCA, 2018, Creighton *et al.*, 2017) was rarely addressed explicitly. This could be because the broader literature on the issue of EAS and suicide was excluded by our search criteria, or it could be a gap in the current debate.

Trends in the debate and future directions

The debate over EAS in persons with psychiatric disorders is likely to continue, as it started to intensify only fairly recently. We found that most articles (81%) were written in 2013 or later, despite the fact the Chabot case occurred over 25 years ago. This may reflect the relatively recent increase in the number of psychiatric EAS cases since 2011, with empirical papers providing a

more detailed account on the practice raising rapidly only since 2015. Psychiatrists remain divided over the issue in the Netherlands and Belgium (Haekens *et al.*, 2017, Pronk *et al.*, 2019). This could relate to our finding that the *ethical* debate is in its relatively early stages. In fact, the low overall direct engagement between authors (9% of mentions) suggests more time and research is needed for the debate to develop further.

Current controversies place parity at the center of an international debate (North-America, Europe and Australia) involving scholars from both clinical and nonclinical backgrounds. If parity arguments rely on physical and mental disorders being similar, some questions will need further study, such as whether mental disorders differ from physical ones, and if so how. There is a longstanding and ongoing dispute about psychiatric diagnosis and prognosis prediction, including in countries allowing for psychiatric EAS based on parity (Allsopp *et al.*, 2019, Insel *et al.*, 2010, Kendler, 2019, van Os *et al.*, 2019, Vanheule *et al.*, 2019). However, conceptual questions of parity may not be sufficient grounds for a safe practice, as suggested by the fact that guidelines developed in the Netherlands and Belgium often contain additional and more stringent criteria than the law itself. Other important empirical, policy questions of parity need further study, e.g., whether diagnosis and prognosis in psychiatry can, similarly to staging systems in physical illness, be valid and reliable. Furthermore, how some of the consequences of allowing psychiatric EAS may play out (on e.g. the patient-physician relationship, mental health care practice and policy, or suicide rates) needs more research, including monitoring of the practice of psychiatric EAS and some of its policy considerations pointed to by both sides of the debate.

Finally, we found that reasons provided by non-clinicians, mostly in favor of psychiatric EAS, have been laid out in more full-length articles, while clinicians have expressed their view more commonly in shorter, reactive articles. It could be that authors against the practice writing longer articles argued against EAS in general (therefore against psychiatric EAS as well) were excluded by our search criteria. However, surveys show that among clinicians, e.g. in the Netherlands and Canada, there is significantly more support for EAS in terminal and physical illness than for psychiatric EAS (Bolt *et al.*, 2015, Rousseau *et al.*, 2017). Our review suggests more thorough input, perhaps through full-length publications from this group, may further inform the debate

about issues that are currently only briefly addressed. Both sides of the debate may benefit from more engagement by mental health professionals other than physicians. Finally, more input from patients e.g. through empirical research focusing on their perspectives, is needed to further inform the ethical debate.

Limitations and strengths

Because articles specifically engaged in the psychiatric EAS debate tended to make conditional arguments (i.e., assuming that EAS is permissible for terminal and physical illness), our review does not speak to reasons that are more generally applicable to EAS per se. But this is a feature of the current literature on psychiatric EAS rather than a limitation of our methods. Second, qualitative coding requires judgment. We recognize that others might have grouped the domains differently: e.g. parity-type reasons occurred across domains. Instead of creating one very large domain, we chose to group the most prominent of these (parity of mental and physical) in order to highlight the different topics per content domain. Hence, there may be some overlap between domains. Another example is the notably rare issue of voluntariness, which we subsumed under the decisional capacity domain, even though it is part of the broader concept of an informed request, as this is where it fit more closely. Furthermore, voluntariness and decisional capacity are often considered together in psychiatric EAS laws and guidelines (EuthanasiaCode, 2018, Griffith *et al.*, 2008, Jones *et al.*, 2017). Hence, the process of categorization was the result of interpretation. However, a strength was that the systematic search strategy covered bioethics literature written by both clinicians and non-clinicians, and data extraction was performed by two independent reviewers. Finally, we did not provide qualitative judgments of the reasons, as the primary intent of a systematic review of reasons is to provide a descriptive overview of the debate (Sofaer and Strech, 2012). Therefore, the most commonly presented reasons are not necessarily the strongest or soundest arguments; however, they are likely to have had a greater presence in the debate.

Conclusion

Psychiatric EAS continues to pose important ethical and policy challenges. This review shows that the current debate is in its relatively early stage. As the number of cases increase in countries

allowing the practice, with more empirical data becoming available, more direct engagement is needed to address conceptual questions and public policy considerations. This in turn will inform policy-making for jurisdictions that consider legalizing the practice.

Table 3.1. Comparison of psychiatric EAS practice across jurisdictions[a]

Country	Year	Voluntary/well-considered request criterion	Unbearable suffering criterion	Irremediability criterion	Specific waiting period	Psychiatric consult required	Guidelines for psychiatric EAS practice
The Netherlands	2002[b]	Voluntary and well-considered[c]	Unbearable suffering without prospect of improvement	No reasonable alternative	No	No[d]	Berghmans *et al*., 2009; Swildens-Rozendaal & van Wersch, 2015; EuthanasiaCode, 2018; NVVP, 2018
Belgium	2002	Voluntary, well-considered, repeated, and without external pressure	Constant, unbearable physical or mental suffering that cannot be alleviated	No reasonable alternative Serious and incurable nature of disorder	Yes, 1 month (for all non-terminally ill patients)	Yes	Brothers of Charity, 2017; Vandenberghe *et al*., 2017; Gastmans, 2018; Orde der Artsen, 2019
Luxembourg	2009	Voluntary, deliberate and repeated	Constant unbearable physical or mental suffering	Incurable medical situation without prospect of improvement	No	No	No
Switzerland	1942	None	None[e]	None[e]	No	No[d]	SAMS, 2018
Germany	2015	None	None	None	No	No	No

Canada	2016[f]	Voluntary request, not the result of external pressure	Enduring physical or psychological suffering	Grievous and irremediable condition	Yes, 10 days (for all EAS cases)	No	No

[a] Refers to psychiatric EAS in persons who are not at end of life (due to other medical conditions). The Benelux countries allow for both euthanasia and assisted suicide. The Belgian Act does not explicitly mention assisted suicide but it is allowed in practice. Switzerland and Germany do not have a specific EAS law but decriminalized assisted suicide (not euthanasia) under certain conditions, regardless of proximity to death and there have been cases of psychiatric EAS in these countries (Griffith *et al*. 2008, Black, 2012, Bruns *et al*., 2016)

[b] Psychiatric EAS in particular became effectively legal following the 1994 Chabot court case involving the assisted suicide of a 50y old woman with complex bereavement who refused treatment (Griffith *et al*. 2008).

[c] While the law does not mention it, the Euthanasia Review Committees (EuthanasiaCode, 2018) add in their definition of the requirement that it be 'without external pressure'.

[d] A psychiatric consultation is not stated in the law but is required by the Euthanasia Review Committees in the Netherlands (Berghmans *et al*. 2009, EuthanasiaCode 2018) and by the Swiss Federal Supreme Court following the 2006 Haas case ruling in Switzerland (Black, 2012).

[e] Although the Swiss law does not have an unbearable suffering or irremediability requirement, the guidelines by the Swiss Academy of Medical Sciences do (SAMS, 2018).

[f]The 2016 Medical Assistance in Dying law (MAID) applies to persons whose natural death is "reasonably foreseeable". Hence, it allows for EAS on the sole basis of a psychiatric disorder only if the person is deemed to have a "reasonably foreseeably death" (CCA, 2018). However, However, a recent Quebec court case ruling that this requirement is unconstitutional suggests that psychiatric EAS will likely become legal in all of Canada (Rukavina, 2019).

Figure 3.1. PRISMA flow chart of the selection process.

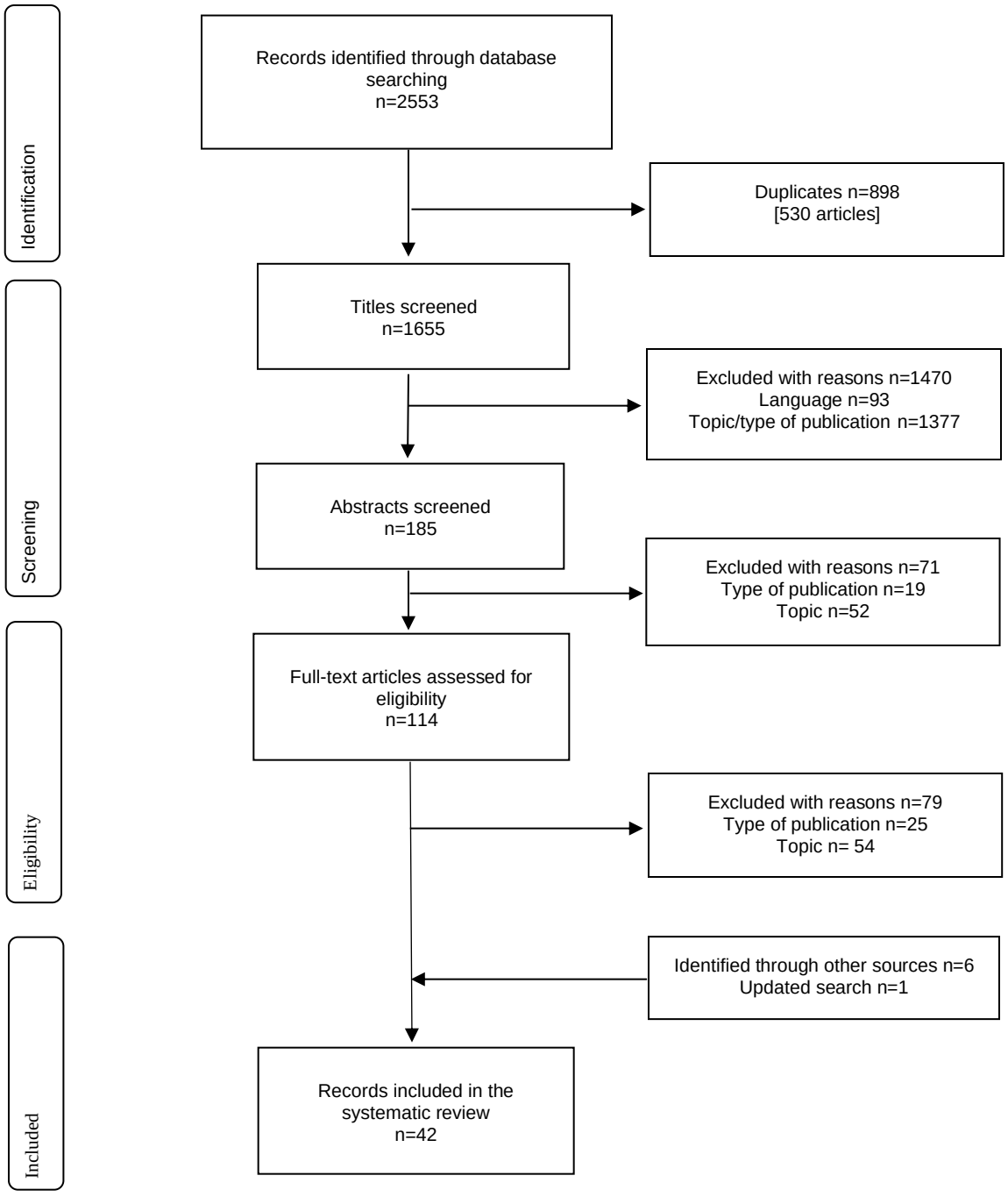

Figure 3.2. Number of mentions per content domain.

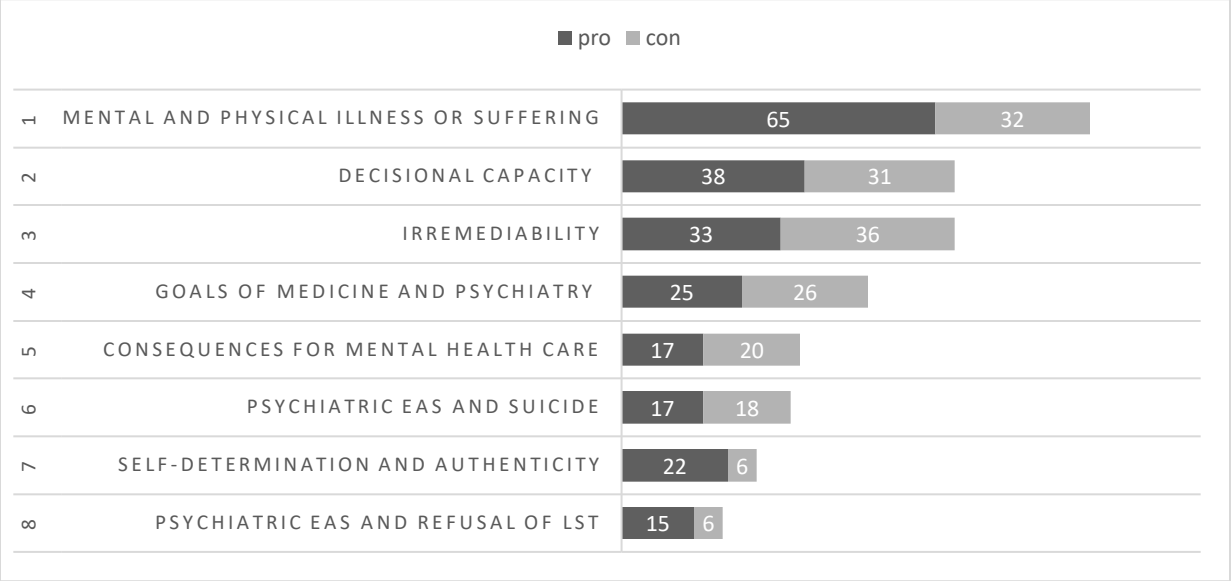

Table 3.2. Domains, subdomains and their reasons.				
Domain	**Side**	**Subdomain and Reasons**	**N**	**Reference**
Mental and physical		**Parity between mental and physical illness or suffering**	**59**	
		Mental and physical illness	**34**	
	Pro	What justifies EAS in the terminally, physically ill (autonomy, irremediable suffering) can be present in mental illness too, hence excluding the mentally ill is discriminatory	8	(Cholbi, 2013, Dembo et al., 2018, Provencher-Renaud et al., 2019, Rooney at al., 2018, Schuklenk and van de Vathorst, 2015a, b, Steinbock, 2017, Tanner, 2018)
		Excluding the mentally ill forces patients to suffer for much longer than those who are terminally ill	5	(Rooney at al., 2018, Sagan, 2015, Schuklenk and van de Vathorst, 2015a, Steinbock, 2017, Varelius, 2016a)
		Excluding the mentally ill based on 'vulnerability' is discriminatory and stigmatizing	5	(Dembo et al., 2018, Hirsch, 2016, Reel, 2018, Rooney at al., 2018, Sagan, 2015)
		Since there are no logical differences between physical and mental illness, there is a strong case for the acceptability of psychiatric EAS	1	(Parker, 2013)
		Mental illness can also be terminal (i.e. what makes a person's condition terminal is whether a decision about ending one's life would have occurred were it not for the person's condition)	1	(Cholbi, 2013)
	Con	Mental illness is distinct from physical illness because its etiology is poorly understood and diagnosis is purely descriptive, hence predictions are less reliable than for physical illness	6	(Blikshavn et al., 2017, den Hartogh, 2015, Kelly, 2017, Kelly and McLoughlin, 2002, Naudts et al., 2006, Pearce, 2017)
		Mental illness (and suffering) is more multifactorial in nature than physical illness (e.g. poor social	5	(Kelly, 2017, Naudts et al., 2006, Pearce,

		conditions), hence we should not treat them in the same way		2017, Schoevers et al., 1998, Simpson, 2018)
		Unfair discrimination only applies if there are no relevant differences between 2 groups, but there are differences (e.g., elevated risk of incapacity, greater risk of error)	2	(Jansen et al., 2019, Steinbock, 2017)
		There is an accepted differential treatment already, since we restrict EAS in the terminally ill to only persons who have capacity	1	(Jansen et al., 2019)
		Mental and physical suffering	**25**	
	Pro	Mental suffering can be as bad as or worse than physical suffering	10	(Cholbi, 2013, Dembo et al., 2018, Dembo, 2010, Hirsch, 2016, Parker, 2013, Provencher-Renaud et al., 2019, Sagan, 2015, Steinbock, 2017, Tanner, 2018, Varelius, 2016b)
		Excluding the mentally ill is unjust because it amounts to discounting their pain	4	(Cholbi, 2013, Provencher-Renaud et al., 2019, Schuklenk and van de Vathorst, 2015a, Tanner, 2018)
		It is up to the patient to determine what unbearable suffering is, regardless of whether the suffering is physical or mental	4	(Cholbi, 2013, Dembo et al., 2018, Player, 2018, Tanner, 2018)
		Mental and physical suffering cannot be disentangled	2	(Cholbi, 2013, Tanner, 2018)
		Mental suffering can be unbearable or rob an individual of a future life of value	2	(Cholbi, 2013, Tanner, 2018)
		Persons typically ask for EAS for reasons other than physical pain (e.g. loss of dignity), so the reasons already include psychological states of mind	1	(Schuklenk and van de Vathorst, 2015a)
		The suffering of incapacitated persons can be worse than that of persons with capacity	1	(Varelius, 2016b)

	Con	In mental illness, the perceived intolerability of suffering may be a symptom of the disorder	1	(Appelbaum, 2018)
		Policy concerns	**38**	
	Pro	The possibility of error (i.e. false positives) can be reduced by adopting rigorous safeguards (e.g. use of reliable tools to assess eligibility, prospective review process, a parallel focus on treatment)	9	(Dembo et al., 2018, Player, 2018, Provencher-Renaud et al., 2019, Rooney at al., 2018, Sagan, 2015, Schuklenk and van de Vathorst, 2015a, b, Vandenberghe, 2011, 2018)
		The possibility of error (i.e. false positives) is present in any medical regimen, we should tolerate a number of false positives to reduce overall suffering	7	(Cholbi, 2013, Provencher-Renaud et al., 2019, Reel, 2018, Rooney at al., 2018, Sagan, 2015, Schuklenk and van de Vathorst, 2015b, Tanner, 2018)
		Greater prognostic uncertainty in psychiatric illness is not a sufficient justification for excluding the mentally ill	3	(Player, 2018, Schuklenk and van de Vathorst, 2015a, Steinbock, 2017)
		Patients should not bear the consequences of lesser diagnostic reliability in mental illness compared to physical illness	2	(Parker, 2013, Schuklenk and van de Vathorst, 2015a)
	Con	Policy considerations require that we err on the side of safety because the risk of false positives is greater than false negatives in non-terminal illness (e.g. due to broad eligibility requirements, capacity assessments not always carried out rigorously)	10	(Appelbaum, 2018, Cowley, 2013, 2015, den Hartogh, 2015, Jansen et al., 2019, Kim and Lemmens, 2016, Miller and Appelbaum, 2018, Schoevers et al., 1998, Steinbock, 2017, Vandenberghe, 2018)

		Whether restricting access to EAS to the terminally ill is justified also depends on policy considerations such as the potential for error	5	(Appelbaum, 2018, Jansen et al., 2019, Kim and Lemmens, 2016, Miller, 2015, Steinbock, 2017)
		Improving the effectiveness of safeguards to reduce false positives may not be feasible	2	(Jansen et al., 2019, Steinbock, 2017)
Decisional capacity		**Existence, nature and determination of competent requests**	**33**	
	Pro	Not all patients with mental illness lack decisional capacity	9	(Dembo et al., 2018, Frati et al., 2014, Hirsch, 2016, Player, 2018, Provencher-Renaud et al., 2019, Schuklenk and van de Vathorst, 2015a, b, Steinbock, 2017, Tanner, 2018)
		A death wish can be a competent wish even in persons with mental illness	5	(Berghmans et al., 2013, Dembo, 2010, Hirsch, 2016, Schuklenk and van de Vathorst, 2015b, Tanner, 2018)
		Excluding the mentally ill amounts to presuming they are incompetent	3	(Dembo et al., 2018, Dembo, 2010, Rooney at al., 2018)
	Con	Some patients with mental illness have impaired capacity and clinicians may not be able to reliably determine whether the request is part of the disorder or not	13	(Appelbaum, 2017, 2018, Blikshavn et al., 2017, Broome and de Cates, 2015, den Hartogh, 2015, Frati et al., 2014, Jansen et al., 2019, Kim and Lemmens, 2016, Miller and Appelbaum, 2018, Olié and Courtet, 2016, Pearce, 2017, Schoevers et al.,

				1998, Steinbock, 2017)
		Not all the mentally ill lack decisional capacity, but we should be extra cautious	3	(den Hartogh, 2015, Frati et al., 2014, Jansen et al., 2019)
		Evaluation of decisional capacity	**25**	
	Pro	Capacity assessments for psychiatric EAS are not different than other capacity assessments (e.g. assessing capacity to refuse life-sustaining treatment)	4	(Parker, 2013, Rooney at al., 2018, Steinbock, 2017, Tanner, 2018)
		We can use trained clinicians or tools to limit the margin of error in capacity assessments	3	(Cholbi, 2013, Rooney at al., 2018, Tanner, 2018)
		A capacity assessment should be unrelated to whether the clinician endorses the decision	2	(den Hartogh, 2015, Hirsch, 2016)
		Clinicians, not the patients, should bear the burden of proof for incapacity (i.e., look for positive evidence of capacity)	2	(Parker, 2013, Steinbock, 2017)
		A cooling off period will ensure a person's request is persistent	2	(Player, 2018, Provencher-Renaud et al., 2019)
		Not acknowledging the potential benefits of treatment should not by itself be considered a failure to appreciate	1	(Player, 2018)
	Con	Persons with mental illness may often change their minds about the request	5	(den Hartogh, 2015, Frati et al., 2014, Jansen et al., 2019, Kelly and McLoughlin, 2002, Olié and Courtet, 2016)
		Persons with mental illness may not meet the "appreciation" requirement for capacity (i.e. how information applies to oneself in estimating their chances of recovery)	3	(Blikshavn et al., 2017, Broome and de Cates, 2015, Steinbock, 2017)
		Affective states can influence capacity	2	(den Hartogh, 2015, Frati et al., 2014)
		Persistence over time does not guarantee a competent request	1	(Schoevers et al., 1998)
		Threshold for evaluation of decisional capacity	**10**	

	Pro	The standards of decisional capacity should be independent of the stakes	4	(Parker, 2013, Player, 2018, Schuklenk and van de Vathorst, 2015a, Tanner, 2018)
		Applying a higher threshold to decisional capacity is better than banning psychiatric EAS altogether	2	(Player, 2018, Rooney at al., 2018)
		In extreme cases, it may be permissible to lower standards of decisional capacity	1	(den Hartogh, 2015)
	Con	The standard of decisional capacity should be higher because the stakes are higher	3	(Cowley, 2015, den Hartogh, 2015, Frati et al., 2014)
		Voluntariness of request	**1**	
	Con	There can be undue external pressure influencing a person's choice	1	(de Kort, 2015)
Irremediability		**Existence, nature, and determination of irremediable cases**	**39**	
	Pro	In some cases, mental illness or suffering is indeed treatment-refractory or incurable	8	(Dembo, 2010, Player, 2018, Reel, 2018, Rooney at al., 2018, Sagan, 2015, Schuklenk and van de Vathorst, 2015a, Tanner, 2018, Vandenberghe, 2018)
		We can reliably determine irremediability and prognosis in psychiatry	3	(Provencher-Renaud et al., 2019, Rooney at al., 2018, Tanner, 2018)
		Prognostic uncertainty is not specific to psychiatry	1	(Steinbock, 2017)
	Con	We cannot reliably determine irremediability and prognosis in psychiatry	18	(Appelbaum, 2017, Blikshavn et al., 2017, Broome and de Cates, 2015, Cowley, 2013, 2015, Jansen et al., 2019, Kelly, 2017, Kelly

				and McLoughlin, 2002, Kim and Lemmens, 2016, Kissane and Kelly, 2000, Miller, 2015, Naudts et al., 2006, Olié and Courtet, 2016, Schoevers et al., 1998, Simpson, 2018, Steinbock, 2017, Vandenberghe, 2011, 2018)
		Recovery in psychiatry can also depend on patient, therapist or external factors, making determination of irremediability difficult	8	(Blikshavn et al., 2017, Cowley, 2013, Jansen et al., 2019, Kelly, 2017, Kissane and Kelly, 2000, Miller and Appelbaum, 2018, Pearce, 2017, Schoevers et al., 1998)
		Given the prognostic uncertainty, hope has important therapeutic value	1	(Blikshavn et al., 2017)
		Patients' subjective v. clinicians' objective judgment of irremediability	**18**	
	Pro	Patients can and should be able to make their own reasonable judgment about chances of recovery (e.g. what treatment should be considered futile)	10	(Berghmans et al., 2013, Cholbi, 2013, Dembo et al., 2018, Dembo, 2010, Parker, 2013, Reel, 2018, Rooney at al., 2018, Schuklenk and van de Vathorst, 2015a, Steinbock, 2017, Tanner, 2018)
		Feelings of hopelessness and demoralization are not necessarily part of the mental disorder	1	(Berghmans et al., 2013)

	Con	We should not only rely on patient judgment in determining irremediability	5	(Appelbaum, 2017, 2018, Cowley, 2013, Jansen et al., 2019, Vandenberghe, 2018)
		Feelings of hopelessness and demoralization can be part of the mental disorder	2	(Appelbaum, 2017, Kim and Lemmens, 2016)
		Waiting for new treatments	**8**	
	Pro	The possibility of future treatment options does not mean patients should wait indefinitely	6	(Berghmans et al., 2013, Dembo et al., 2018, Schuklenk and van de Vathorst, 2015a, Steinbock, 2017, Tanner, 2018, Varelius, 2016b)
	Con	New treatments may be discovered in the near future (e.g. ketamine)	2	(Broome and de Cates, 2015, Simpson, 2018)
Goals of medicine & psychiatry		**Patient-physician relationship in psychiatry**	**27**	
	Pro	An open attitude towards psychiatric EAS can in itself be therapeutic for patients	5	(Hirsch, 2016, Player, 2018, Provencher-Renaud et al., 2019, Reel, 2018, Vandenberghe, 2018)
		A psychiatric EAS request should be explored on its own terms and not be interpreted as a cry for help only	4	(Naudts et al., 2006, Parker, 2013, Vandenberghe, 2011, Vink, 2012)
		A physician's attitude of unconditionally preserving life may not foster good care	2	(Dembo, 2010, Vandenberghe, 2011)
		Physicians can give up on patients even when psychiatric EAS is not allowed	1	(Rooney at al., 2018)
		A physician's excessive identification with the patient can be avoided	1	(Berghmans et al., 2013)

	Con	A psychiatric EAS request can carry other meanings than a wish to die that can be responded to without endorsing psychiatric EAS	5	(Blikshavn et al., 2017, Miller, 2015, Olié and Courtet, 2016, Schoevers et al., 1998, Vandenberghe, 2011)
		Allowing psychiatric EAS might cause physicians to give up on their patients	4	(Appelbaum, 2017, 2018, Blikshavn et al., 2017, Miller and Appelbaum, 2018)
		Allowing psychiatric EAS can negatively impact the patient-physician relationship, e.g. by undermining hope	3	(Blikshavn et al., 2017, Schoevers et al., 1998, Vandenberghe, 2011)
		Allowing psychiatric EAS may reinforce avoidance rather than coping with psychological pain	1	(Blikshavn et al., 2017)
		A physician's excessive identification can impact the evaluation process	1	(Schoevers et al., 1998)
		Compatibility with the goals of medicine & psychiatry	**24**	
	Pro	Physicians including psychiatrists have an obligation to relieve their patients' suffering, hence compassion can justify psychiatric EAS	7	(Berghmans et al., 2013, Dembo, 2010, den Hartogh, 2015, Hirsch, 2016, Parker, 2013, Schuklenk and van de Vathorst, 2015b, Tanner, 2018)
		Providing psychiatric EAS can be compatible with the goals of medicine and psychiatric practice	5	(Berghmans et al., 2013, den Hartogh, 2015, Parker, 2013, Steinbock, 2017, Vandenberghe, 2018)
	Con	Providing psychiatric EAS is not compatible with the goals of medicine and psychiatric practice	11	(de Kort, 2015, Jansen et al., 2019, Kelly, 2017, Kim and Lemmens, 2016,

				Kissane and Kelly, 2000, Miller, 2015, Naudts et al., 2006, Olié and Courtet, 2016, Schoevers et al., 1998, Simpson, 2018, Vink, 2012)
		A right to medical treatment does not entail a right to assistance with suicide	1	(Jansen et al., 2019)
Consequences for mental health care		**Effects on mental health care**	**19**	
	Pro	Allowing psychiatric EAS and improving mental health care (e.g. improving funding and access to mental health care, reducing stigma, improving prevention) are not mutually exclusive	7	(Provencher-Renaud et al., 2019, Reel, 2018, Rooney at al., 2018, Sagan, 2015, Schuklenk and van de Vathorst, 2015a, Tanner, 2018, Vandenberghe, 2011)
	Con	Allowing psychiatric EAS will have negative consequences for mental health care policy (e.g. it may reinforce poor expectations towards mental health care)	8	(Appelbaum, 2017, 2018, Blikshavn et al., 2017, Kissane and Kelly, 2000, Miller and Appelbaum, 2018, Naudts et al., 2006, Olié and Courtet, 2016, Simpson, 2018)
		Allowing psychiatric EAS should depend on whether other factors can be addressed first (e.g. improving funding and access to mental health care)	4	(Appelbaum, 2017, de Kort, 2015, Pearce, 2017, Simpson, 2018)
		Consequences for vulnerable populations	**18**	
	Pro	There is little empirical evidence that psychiatric EAS will have negative consequences for vulnerable populations	5	(Cholbi, 2013, Dembo et al., 2018, Dembo, 2010,

				Steinbock, 2017, Varelius, 2016a)
		Allowing psychiatric EAS will not necessarily negatively impact families	3	(Provencher-Renaud et al., 2019, Rooney at al., 2018, Sagan, 2015)
		Expansion of psychiatric EAS to other conditions or existential suffering is an inevitable, but not necessarily bad, consequence	2	(Provencher-Renaud et al., 2019, Steinbock, 2017)
	Con	Allowing psychiatric EAS may have negative consequences for vulnerable populations or suggest that their situation can be hopeless	6	(Appelbaum, 2018, Frati et al., 2014, Jansen et al., 2019, Kim and Lemmens, 2016, Schoevers et al., 1998, Simpson, 2018)
		Allowing psychiatric EAS may negatively impact patients' families	2	(Appelbaum, 2017, Pearce, 2017)
Psychiatric EAS & suicide		**Compatibility with the duty to prevent suicide**	**26**	
	Pro	Psychiatric EAS is a more humane alternative to suicide and hence can prevent violent or lonely suicides	10	(Berghmans et al., 2013, Dembo et al., 2018, Dembo, 2010, Naudts et al., 2006, Provencher-Renaud et al., 2019, Reel, 2018, Sagan, 2015, Schuklenk and van de Vathorst, 2015b, Steinbock, 2017, Vandenberghe, 2011)
		Denying access to psychiatric EAS forces people to attempt or commit suicide	2	(Provencher-Renaud et al., 2019, Sagan, 2015)
	Con	Psychiatric EAS conflicts with the duty to prevent suicide	6	(Frati et al., 2014, Miller and Appelbaum, 2018, Naudts et al., 2006, Pearce, 2017, Simpson, 2018,

				Vandenberghe, 2011)
		Just because suicide is no longer illegal does not mean there is a right to assistance with suicide	5	(Cowley, 2015, de Kort, 2015, Jansen et al., 2019, Simpson, 2018, Vink, 2012)
		The likelihood or threat of a suicide attempt is not a reason to provide psychiatric EAS	2	(Cowley, 2013, 2015)
		Denying EAS to the mentally ill does not force these patients to commit suicide	1	(Cowley, 2015)
		Ability to end one's own life	**9**	
	Pro	Patients should not be denied access to psychiatric EAS just because they are able to end their own lives	3	(Dembo et al., 2018, Player, 2018, Reel, 2018)
		Not all patients are physically able or have the means to commit suicide	2	(Sagan, 2015, Schuklenk and van de Vathorst, 2015b)
	Con	If persons have other ways to end their lives, assistance of physicians is not needed	4	(den Hartogh, 2015, Jansen et al., 2019, Simpson, 2018, Vink, 2012)
Self-determination & authenticity		**Self-determination**	**22**	
	Pro	Persons, including those with mental illness, can have a rational wish to die	9	(Berghmans et al., 2013, Dembo, 2010, Frati et al., 2014, Parker, 2013, Provencher-Renaud et al., 2019, Schuklenk and van de Vathorst, 2015b, Steinbock, 2017, Tanner, 2018, Vandenberghe, 2018)
		Persons are free to make their own choices, even if these are irrational	6	(Cholbi, 2013, Hirsch, 2016,

				Parker, 2013, Provencher-Renaud et al., 2019, Steinbock, 2017, Varelius, 2016b)
		Autonomy should be respected provided the person has capacity	3	(Frati et al., 2014, Rooney at al., 2018, Steinbock, 2017)
	Con	Respect for autonomy by itself does not justify psychiatric EAS	3	(den Hartogh, 2015, Jansen et al., 2019, Simpson, 2018)
		The meaning of 'rational' is problematic when applied to a wish to die	1	(Broome and de Cates, 2015)
		Authenticity & personal integrity	**6**	
	Pro	Not being able to live up to our goals and values (loss of integrity) due to mental illness can make life not worth living	2	(Dembo, 2010, Wijsbek, 2012)
		A person's values are what matters in a personal choice	1	(Cholbi, 2013)
		Depression can be a part of one's authentic self	1	(Schuklenk and van de Vathorst, 2015a)
	Con	Depression may not be compatible with an authentic choice	1	(Cowley, 2015)
		Personal integrity does not solely depend on whether or not we are able to live up to our goals and values	1	(Cowley, 2013)
Psychiatric EAS & LST refusal		**Moral relationship between EAS and refusal of LST**	**21**	
	Pro	If we allow refusal/withdrawal of LST in psychiatric patients, we should allow psychiatric EAS too	7	(Dembo et al., 2018, Parker, 2013, Player, 2018, Reel, 2018, Tanner, 2018, Varelius, 2016a, Varelius, 2016b)
		If refusal/withdrawal of LST in psychiatric patients and psychiatric EAS are morally equivalent, the same conditions should apply (e.g. whether other treatments exist or whether the patient suffers should not matter)	3	(Player, 2018, Steinbock, 2017, Varelius, 2016b)
		Potential negative aspects of psychiatric EAS (e.g. danger of hasty decision, futility, false positives,	2	(Varelius, 2016a, Varelius, 2016b)

		degree of physician involvement) also apply to refusal/withdrawal of LST		
		Since we allow withdrawal of LST after a suicide attempt, we should allow psychiatric EAS too	1	(Varelius, 2016b)
		Denying access to psychiatric EAS based on vulnerability would justify denying the right to refuse LST	1	(Rooney at al., 2018)
		Respect for refusal of LST is better justified in terms of well-being and autonomy than bodily integrity	1	(Varelius, 2016a) Varelius, 2016a)
	Con	The negative right to refusal of LST (a physician's obligation to respect a patient's bodily integrity) is not the same as a positive right to assisted death	3	(Jansen et al., 2019, Miller, 2015, Steinbock, 2017)
		The distinction between acts and omissions does not apply in psychiatry and suicide prevention (i.e. allowing a patient to commit suicide amounts to being guilty of medical misconduct	2	(Frati et al., 2014)
		The doctrine of double effect is not helpful in psychiatric disorders, i.e. we do not treat mental distress with drugs that could hasten death (as an indirect effect)	1	(Kelly and McLoughlin, 2002)
		EAS is different than refusal of LST because it requires physician assistance	1	(Jansen et al., 2019)

Appendix 3A. Search terms and full search strategy per database.

Search terms used		
Group A	**Group B**	**Group C**
euthanasia assisted suicide assisted death physician-assisted suicide physician-assisted death aid in dying medical assistance in dying assisted dying mercy killing death with dignity	mental illness mentally ill mental disorder psychiatry psychiatric disorder depression depressive non-terminal nonterminal	ethics ethical philosophy philosophical bioethics bioethical moral morals

Search strategy per database	
Medline	
Interface	PubMed
Database	MEDLINE
Date of search	Inception to Nov,6 2018
Limits	None
Search strategy	
("Suicide, Assisted"[Mesh] OR "Euthanasia"[Mesh] OR euthanasia[Title/Abstract] OR assisted suicide [Title/Abstract] OR assisted death [Title/Abstract] OR assisted deaths[tiab] OR “physician-assisted suicide” [Title/Abstract] OR “physician-assisted death” OR “aid in dying”[Title/Abstract] OR “medical assistance in dying” [Title/Abstract] OR mercy killing[tiab] OR “death with dignity”[tiab] OR euthanize*[tiab])AND ("Mental Disorders"[Mesh] OR mental illness[Title/Abstract] OR mentally ill[Title/Abstract] OR mental disorder [Title/Abstract] OR mental illnesses[tiab] OR mental disorders[tiab] OR psychiatr*[Title/Abstract] OR psychiatric disorder[Title/Abstract] OR non-terminal[Title/Abstract] OR nonterminal[Title/Abstract]) AND ("Ethics"[Mesh] OR "Philosophy"[Mesh] OR ethic* OR philosophy OR bioethic*[tiab] OR philosophical[tiab] OR moral[tiab] OR morals[tiab])	
Records retrieved: 931	
Web of Science	
Interface	
Database	Web of Science
Date of search	Inception to Nov,6 2018
Limits	None
Search strategy	
TS=(euthanasia OR assisted suicide OR assisted death OR physician-assisted suicide OR physician-assisted death OR aid in dying OR medical assistance in dying OR assisted dying OR mercy killing OR death with dignity) AND TS=(mental illness OR mentally ill OR mental disorder OR psychiatry OR psychiatric disorder OR depression OR depressive OR non-terminal OR nonterminal) AND TS=(ethics OR ethical OR philosophy OR philosophical OR bioethics OR bioethical OR moral OR morals)	
Records retrieved: 204	
Embase	
Interface	
Database	Embase
Date of search	Inception to Nov,6 2018
Limits	None
Search strategy	
('euthanasia'/exp OR 'euthanasia' OR 'assisted suicide'/exp OR 'assisted suicide' OR 'euthanasia':ab,ti,kw OR 'assisted suicide':ab,ti,kw OR 'assisted death':ab,ti,kw OR 'physician-assisted suicide':ab,ti,kw OR 'physician-assisted death':ab,ti,kw OR 'aid in dying':ab,ti,kw OR 'medical assistance in dying':ab,ti,kw OR 'assisted dying':ab,ti,kw OR 'mercy killing':ab,ti,kw OR 'death with dignity’:ab,ti,kw) AND ('psychiatry'/exp OR 'mental illness':ab,ti,kw OR 'mentally ill':ab,ti,kw OR 'mental disorder':ab,ti,kw OR 'psychiatry':ab,ti,kw OR 'psychiatric disorder':ab,ti,kw OR 'depression':ab,ti,kw OR 'depressive':ab,ti,kw OR 'non-terminal':ab,ti,kw OR 'nonterminal':ab,ti,kw) AND ('ethics'/exp OR 'ethics' OR 'philosophy'/exp OR 'ethics':ab,ti,kw OR 'ethical':ab,ti,kw OR 'philosophy':ab,ti,kw OR 'philosophical':ab,ti,kw OR 'bioethics':ab,ti,kw OR 'bioethical':ab,ti,kw OR 'moral':ab,ti,kw OR 'morals':ab,ti,kw)	
Records retrieved: 541	

PsycInfo	
Interface	
Database	PsycInfo
Date of search	Inception to Nov,6 2018
Limits	None
Search strategy	
((IndexTermsFilt: ("Euthanasia") OR IndexTermsFilt: ("Assisted Suicide")) OR (abstract: (euthanasia)) OR (abstract: (assisted suicide)) OR (abstract: (physician-assisted suicide)) OR (abstract: (physician-assisted death)) OR (abstract: (aid in dying)) OR (abstract: (medical assistance in dying)) OR (abstract: (mercy killings)) OR (abstract: (death with dignity))) AND ((IndexTermsFilt: ("Psychiatry") OR IndexTermsFilt: ("Mental Disorders")) OR (abstract: (mental illness)) OR (abstract: (mentally ill)) OR (abstract: (psychiatry)) OR (abstract: (psychiatric disorder)) OR (abstract: (depression)) OR (abstract: (depressive)) OR (abstract: (non-terminal)) OR (abstract: (nonterminal))) AND ((IndexTermsFilt: ("Bioethics") OR IndexTermsFilt: ("Ethics") OR IndexTermsFilt: ("Morality")) OR (abstract: (ethics)) OR (abstract: (ethical)) OR (abstract: (philosophy)) OR (abstract: (philosophical)) OR (abstract: (bioethics)) OR (abstract: (moral)))	
Records retrieved: 146	
Scopus	
Interface	
Database	Scopus
Date of search	Inception to Nov,6 2018
Limits	None
Search strategy	
TITLE-ABS-KEY("euthanasia" OR "assisted suicide" OR "assisted death" OR "physician-assisted suicide" OR "physician-assisted death" OR "aid in dying" OR "medical assistance in dying" OR "assisted dying" OR "mercy killing" OR "death with dignity") AND TITLE-ABS-KEY("mental illness" OR "mentally ill" OR "mental disorder" OR "psychiatry" OR "psychiatric disorder" OR "depression" OR "depressive" OR "non-terminal" OR "nonterminal") AND TITLE-ABS-KEY("ethic?" OR "ethical" OR "philosophy" OR "philosophical" OR "bioethics" OR "bioethical" OR "moral" OR "morals")	
Records retrieved: 647	
CINAHL	
Interface	
Database	CINAHL
Date of search	Inception to Nov,6 2018
Limits	None
Search strategy	
(MH "Euthanasia") OR (MH "Suicide, Assisted") OR AB (euthanasia OR assisted suicide OR assisted death OR physician-assisted suicide OR physician-assisted death OR aid in dying OR medical assistance in dying OR assisted dying OR mercy killing OR death with dignity) AND (MH "Mental Disorders") OR (MH "Psychiatric Patients") OR AB (mental illness OR mentally ill OR mental disorder OR psychiatry OR psychiatric disorder OR depression OR depressive OR non-terminal OR nonterminal) AND (MH "Ethics") OR (MH "Bioethics") OR (MH "Philosophy") OR (MH "Philosophy, Medical") OR AB (ethics OR ethical OR philosophy OR philosophical OR bioethics OR bioethical OR moral OR morals)	
Records retrieved: 51	
Philosopher's Index	
Interface	
Database	Philosopher's Index
Date of search	Inception to Nov,6 2018
Limits	None
Search strategy	
ab(euthanasia OR assisted suicide OR assisted death OR physician-assisted suicide OR physician-assisted death OR aid in dying OR medical assistance in dying OR assisted dying OR mercy killing OR death with dignity) AND ab(mental illness OR mentally ill OR mental disorder OR psychiatry OR psychiatric disorder OR depression OR depressive OR non-terminal OR nonterminal) AND noft(ethics OR ethical OR philosophy OR bioethics OR bioethical OR moral OR morals)	
Records retrieved: 33	

Appendix 3B. Table with country of affiliation of corresponding authors.

Country	**N**	**%**
USA[a]	11	26
Canada[a]	9	21
The Netherlands[b]	6	14
UK	4	10
Australia[a]	2	5
Belgium[b]	2	5
Ireland	2	5
Finland	2	5
France	1	2
Italy	1	2
Poland	1	2
Norway	1	2

[a]Legislation of EAS (terminal illness)
[b]Legislation of EAS (terminal & non-terminal illness)

Chapter 4: Parity Arguments in the Ethical Debate About Psychiatric EAS: Structure and Limits

Nicolini M.E., Gastmans C., Kim S. Y. H. (2019) Parity Arguments for 'Physician Aid-in-Dying' (PAD) for Psychiatric Disorders: Their Structure and Limits. *The American Journal of Bioethics* 19:10, 3-7. https://doi.org/10.1080/15265161.2019.1659606

Abstract

This paper explores the structure and limits of the parity (or "non-discrimination") argument, which figures prominently in the debate about psychiatric EAS. The argument is conditional in nature and relies on four different premises, the truth of each of which is often taken for granted. However, each premise is controversial in itself and needs further justification. The argument's central focus on suffering as the basis for EAS can be questioned, since suffering appears neither a necessary nor a sufficient condition for EAS. Furthermore, the argument emphasis on an ideal scenario tends to disregards the implications for public policy. Without further in-depth analysis of each of its premises, the argument remains rhetorically forceful but unsound.

Introduction

Kious and Battin (K&B) argue that psychiatric PAD (PPAD) should be legal in the US, based on a "parity" argument (Kious and Battin, 2019). This is the most popular approach to argue for PPAD (Cholbi, 2013, Dembo *et al.*, 2018, Dembo, 2010, Hirsch, 2016, Parker, 2013, Provencher-Renaud *et al.*, 2019, Rooney *et al.*, 2018, Schuklenk and van de Vathorst, 2015, Tanner, 2018, Varelius, 2016b). What K&B add is that since, in their view, the parity argument is valid, there is a dilemma because PPAD conflicts with the practice of involuntary commitment in psychiatry. In this editorial, we sketch out the structure of the argument from parity, pointing out its challenges and limits. This will show that the dilemma K&B pose is actually a general problem about PPAD, not a dilemma specific to PPAD and involuntary commitment.

K&B's parity argument has the following form: If PAD for terminal physical illness is justified on the basis of suffering, then fairness/equality/parity/non-discrimination dictates that PPAD be permitted. The argument is forceful but formal. It yields the conclusion that PPAD should be permitted only for those who also believe in four fairly controversial premises, each of which would take considerable work to defend: (P1) PAD of some form should be permitted; (P2) it must be based on suffering; (P3) situations of suffering in PAD and in PPAD are so similar such that not permitting PPAD would be arbitrary; (P4) permitting PPAD would not have negative policy and practice implications serious enough to outweigh the intended merits of PPAD. Giving a comprehensive analysis of each claim is beyond the scope of this editorial. Instead, we point out the many points of dispute that still need to be resolved for the parity argument to yield K&B's conclusions.

The conditional nature of parity arguments

As is the case for most articles arguing in favor of PPAD based on the parity argument, the underlying assumption is that PAD for terminal physical illness is legally permitted. Thus it is a conditional argument. As a formal argument, the argument has 3 potential conclusions. One, PPAD is not permissible because PAD and PPAD are different; the parity argument does not carry. Two, PPAD is permissible because it is similar enough to PAD; parity argument carries. Three, PPAD

turns out not to be permissible, but the parity argument still applies, and PAD for terminal illness is impermissible—a possibility that Foster rightly mentions but is rarely explored in parity arguments for PPAD (Foster, 2019)[2].

The meaning of suffering and their uses in the parity argument

Most parity arguments for PPAD assert some version of 'mental suffering is as bad as or worse than physical suffering' (Cholbi, 2013, Dembo *et al.*, 2018, Dembo, 2010, Hirsch, 2016, Parker, 2013, Provencher-Renaud *et al.*, 2019, Sagan, 2015, Steinbock, 2017, Tanner, 2018, Varelius, 2016b). As psychiatrists (MN and SK) we do not disagree with the statement.[3] What we question is the accompanying assertion that to argue against PPAD amounts to not taking suffering seriously (Cholbi, 2013, Kious and Battin, 2019, Provencher-Renaud *et al.*, 2019, Schuklenk and van de Vathorst, 2015, Tanner, 2018). Such an assertion has rhetorical force but cannot support the parity argument since it makes sense only if the parity argument is already seen as valid. After all, it is possible to take mental suffering extremely seriously and non-callously, with skill, empathy, and resources—without permitting PPAD. 'Suffering X is as bad as Y' is a philosopher's shorthand whose meaning and implications depend on how we understand the nature and source of the suffering (De Vries, 2019).

The premise that all PAD regimes must be justified by (alleviating) suffering and the premise that the situations of suffering in terminal PAD and in PPAD are 'similar enough' are inextricably linked: how one defines and understands suffering as the basis for PAD will determine whether and how it can be used in a parity argument. Thus, we examine P2 and P3 together.

---

[2] For example, K&B state, under the section on 'Severity of Suffering': "We would also invite interlocutors to imagine someone with a relatively painless, terminal physical illness who chooses PAD to end or prevent the emotional or existential suffering that her illness brings. If that is justifiable (and it seems to be permitted by PAD statues in the U.S.), PAD in mental illness should sometimes be justifiable, too." If however it turns out there are good reasons to not permit PAD for mental illness, then it would seem the parity argument should persuade K&B that permitting PAD for terminal illness may be a mistake. (We here ignore arguments for PPAD not using the parity argument which are hard to find. Does the relative rarity of such arguments indicate the difficulty of constructing them?)

[3] We have not found a commentator who argues PPAD should not be allowed on the basis that mental suffering is not serious enough.

Is suffering a necessary basis for physician aid-in-dying?

The authors argue that (alleviating) suffering is the moral basis for PAD in all jurisdictions allowing the practice. While suffering is explicitly mentioned among the PAD eligibility requirements of European countries and Canada, it is not generally true of PAD laws in US states. To account for the anomaly of the US laws, K&B speculate (without explaining why such a speculation amounts to an *argument*) that most cases of PAD even in the US are motivated by suffering and argue that the terminal illness requirement is a mere 'safeguard' rather than a partial justification for PAD.

In fact, rather than 'suffering as the basis and terminality as a safeguard,' the Oregon style laws can just as well be interpreted as based on autonomy with terminality as a co-justification. A doctor in Oregon is permitted to provide PAD to a patient (who otherwise meets criteria for PAD) whose reason for requesting PAD is a desire to control his exit from life. Would an advocate of PAD in Oregon think providing PAD to this man violates some principle behind the law? Without having to refer to suffering,[4] one can coherently say: the justification for PAD is that at the end of one's life, how one dies should be determined by the person's 'values and beliefs.' Or, as some have put it, "we want that last act to reflect our own convictions" (Dworkin *et al.*, 1997). This certainly sounds like addressing terminality itself—the fact that one's "very existence as a singular entity is ending"(Bartlett and Finder, 2019)—is the very point of PAD (Bartlett and Finder, 2019, Campbell, 2019, De Vries, 2019, Foster, 2019, Ho and Norman, 2019, Lemmens, 2019).

Indeed, some suffering-based regimes might more accurately be re-framed as 'autonomy-based with suffering as a safeguard' regimes. If a jurisdiction leaves the determination of suffering as the justification for PAD entirely up to the patient, as in Canada, the ultimate justification for PAD seems to be autonomy and such a law, as den Hartogh observes, may only pay "lip-service to its

[4] K&B may object that in our example the person who does not get to control how he dies will experience suffering because of this and that is the basis for allowing PAD. But this is like saying that coercing another person is wrong only because of the suffering it would cause. The determining value is autonomy itself. 'Suffering' by itself is too malleable a label. It can too easily apply to cases we would intuitively resist (Cowley 2013, Lemmens 2019).

commitment to compassion as the basic justifying ground for PAD"(den Hartogh, 2019). In such cases, suffering might better be seen as a safeguard, not a justification.

Is suffering a sufficient basis for physician aid-in-dying?

Even if suffering is taken as the basis for PAD, no suffering-based regime treats alleviation of suffering as a sufficient basis: they all add additional eligibility criteria. These additional restrictions seem just as arbitrary or just as necessary, depending on one's point of view, as the terminal illness requirement; or at least it would require an argument to support either view.

First, PAD based on purely existential suffering without a medical basis (e.g., tired of living or completed life) does not qualify. What is the suffering-based moral principle that excludes all non-medically based suffering as a basis for PAD (Gaignard and Hurst, 2019, Steinbock, 2017)? It is arbitrary and inconsistent to expand the meaning of suffering to include one's inability to exercise control over one's death (as a means of arguing for suffering as basis for PAD) but then to restrict its meaning by insisting that it must be medically based.

Second, in all suffering-based PAD regimes, intractability/irremediability is a requirement. It is a separate, additional restriction (van Veen and van Delden, 2019). But why is irremediability necessary? If the experience of suffering is the same in person A and person B but their prognosis is different (an irremediable condition versus a slow to recover but not irremediable condition), why should only person A qualify?

Third, all PAD regimes permit only voluntary PAD. But a welfare-based justification for PAD, such as suffering (in contrast to an autonomy-based regime), does not rule out non-voluntary PAD (Jones, 2011, Keown, 2002, Varelius, 2016b). One may question why only voluntary PAD should be permitted when two people have identical suffering.

Can the parity argument work when suffering is neither necessary nor sufficient basis for physician aid-in-dying?

First, if suffering is not a necessary basis for PAD, then a suffering-based parity argument is irrelevant. Second, the various extra restrictions on PAD that we observe even in suffering-based regimes clearly violate parity. One might therefore argue that terminality violates parity but is just as necessary; at any rate, if one accepts the other parity-violating restrictions, parity per se would not be an argument against terminality.

But if one maintains the primacy of parity, the differential treatments required by the above restrictions are illegitimate. One would then be committed to expanding PAD to include not only suffering from non-terminal disorders, but also non-medical suffering, non-irremediable suffering, and non-voluntary PAD. Or one might instead, seeing that parity *requires* such an expansion, reject the original premise of permissibility of PAD.

Would consequences of permitting physician aid-in-dying for psychiatric disorders be worrisome enough to counter its intended merits?

Up to this point, we have largely focused on normative, conceptual problems for the parity argument. But (just for the sake of argument) even if we imagine that the parity argument for PPAD were conceptually sounder than it is, the question still remains: how does one justify going from an idealized conceptual argument to a public policy? K&B, like other proponents of the parity argument, write as though showing the philosophical plausibility of PPAD in a single ideal case provides sufficient basis for a public policy (Cholbi, 2013, Dembo *et al.*, 2018, Kious and Battin, 2019, Provencher-Renaud *et al.*, 2019, Rooney *et al.*, 2018, Schuklenk and van de Vathorst, 2015, Steinbock, 2017, Tanner, 2018). But as De Vries reminds us, such arguments are idealized, "with no appreciation of the way such judgments are shaped by the context in which they are made"(De Vries, 2019). Or, as Foster describes it, "considering only that patient is a philosophical indulgence not available to legislators"(Foster, 2019). To be fair, even if some proponents have neglected the real-world context and consequences of normative concepts, other commentators have pointed this out. While some argue that there is no "principled basis" for excluding psychiatric patients (Schuklenk and van de Vathorst, 2015), others state that "there is a gap between acknowledging

that there are cases in which [PPAD] is justified and creating a law or policy that reliably identifies such cases" (den Hartogh, 2015, Steinbock, 2017).

There is a wide range of policy challenges related to allowing and implementing PPAD. The most frequently cited challenge is that there is a greater potential for error in evaluating patients with nonterminal, psychiatric disorders: even if ideal cases exist, there is the question of reliably identifying those cases. As den Hartogh points out, policymakers could reasonably think that no "institutional arrangement will guarantee us to sufficient extent that the exceptional cases are properly identified," hence we should err on the side of safety (den Hartogh, 2015, Foster, 2019, Lemmens, 2019, Miller and Appelbaum, 2018, Steinbock, 2017, Vandenberghe, 2018, Zuradzki and Nowak, 2019). The specific difficulties relate to reliably and objectively assessing irremediability and decision-making capacity in persons with a PPAD request (Broome and de Cates, 2015, den Hartogh, 2015, Lemmens, 2019, Miller and Appelbaum, 2018, Steinbock, 2017, van Veen and van Delden, 2019, Zuradzki and Nowak, 2019). Indeed, what we mean by irremediability and 'treatment-refractory' in psychiatry is ill-defined (Blikshavn *et al.*, 2017, Jansen *et al.*, 2019, Kim and Lemmens, 2016, Kissane and Kelly, 2000, Miller, 2015, Schoevers *et al.*, 1998, Simpson, 2018, Steinbock, 2017) and predictions about prognosis can be unreliable when causation is poorly understood and diagnosis mostly descriptive (Blikshavn *et al.*, 2017, den Hartogh, 2015, Kelly, 2017, Kelly and McLoughlin, 2002, Kendler, 2019, Naudts *et al.*, 2006, Pearce, 2017, Schoevers *et al.*, 1998, Simpson, 2018, van Os *et al.*, 2019). Furthermore, there is a challenge of defining what counts as an informed request for PPAD and how each of the criteria for capacity should be interpreted (Kim, 2016a, Owen, 2016).

Finally, there are broader policy concerns about allowing PPAD and its potential societal consequences: the impact on the patient-physician relationship (Blikshavn *et al.*, 2017, Calkins and Swetz, 2019, Olié and Courtet, 2016, Schoevers *et al.*, 1998) and on the profession of psychiatry (Calkins and Swetz, 2019, Jansen *et al.*, 2019, Kissane and Kelly, 2000, Miller, 2015, Simpson, 2018), the role of social determinants contributing to mental health (Ho and Norman, 2019, Pearce, 2017, Simpson, 2018), and the expressivist consequences such as the implicit

message that may be conveyed to vulnerable populations (Appelbaum, 2018, De Vries, 2019, Foster, 2019, Kim and Lemmens, 2016, Kim, 2019, Le Glaz *et al.*, 2019, Simpson, 2018).

Conclusion

K&B's parity argument is similar to many parity arguments in that it advocates legal policy based on an idealized conceptual argument. What is different about their paper is that, *after* concluding that PPAD should be legal, they *then* go on to consider some serious policy and practice considerations, namely, the problem of involuntary commitment. Indeed, K&B's discussion of the difficulties of using a capacity standard or a suffering metric articulate important policy and practice problems. But that discussion makes perfect sense without juxtaposing it to the issue of involuntary commitment at all. The authors do not see this because, by this point in their paper, they have already accepted the parity argument as valid. They locate the dilemma ('a moral crisis') in the wrong place. Their problem is about PPAD itself.

The parity argument is ultimately a test of the validity of the content that we put in it. If it yields a conclusion that conflicts with our moral and policy considerations, then we should at least revisit the argument's starting point. What we should not do is to be so committed to an outcome of the argument that we lose sight of its double-edged nature.

Chapter 5: Irremediability and Treatment-Resistant Depression: An Evidence-Based Review

Nicolini M.E., Jardas E., Zarate C. A., Gastmans C., Kim S.Y.H. Irremediability and Treatment-Resistant Depression: An Evidence-Based Review [*Manuscript in preparation*]

Abstract

Background: Irremediability (i.e. the lack of remaining treatment options) is a key requirement for psychiatric EAS, and one of the most debated ones. Arguments about irremediability are common in the debate about psychiatric EAS, yet evidence for the empirical claims invoked is often lacking. Through an evidence-based review of the main claims, this paper aims at addressing this gap, focusing on treatment-resistant depression (TRD) as a paradigm case.

Method: A literature review was performed in PubMed based on the following three research questions, reflecting the main empirical arguments in the ethical debate: 1) Is there a uniform definition of TRD; 2) Can we predict group-level long-term outcomes of TRD; and 3) Can we make individual predictions of treatment-resistance in depression.

Results: Regarding the first question, clinical evidence confirms that a single definition of TRD is lacking and discussions about the very conceptualization of TRD in clinical practice and in research are ongoing. As for the second question, the first systematic review on the topic was published in 2011, with only four naturalistic long-term longitudinal studies published after that. Although most patients in these four studies had significant severity of treatment-resistance upon entry to the study, outcomes varied widely. Finally, there is a growing body of evidence assessing the accuracy of individual predictions about treatment resistance, but they vary in sample size and design. While predictive accuracy of machine learning models appears promising, these studies are still considered preliminary.

Conclusion: Irremediability remains at the center of debates about the practice of EAS for psychiatric disorders. The main area of debate concerns the question of whether clinicians can reliably predict chances of recovery in the field of psychiatry. Evidence from the literature on TRD shows that TRD is a heterogenous concept primarily used in research, with relatively little knowledge about long-term outcomes and predictors for TRD at the group-level. While the literature on individual prediction of treatment-resistance in depression using machine learning is exponentially growing, current predictions at the individual level are not yet accurate enough to be used in clinical practice, including in the context of psychiatric EAS.

Introduction

A few countries in the world permit EAS based primarily on a psychiatric disorder (psychiatric EAS), including the Benelux countries and Switzerland (Griffith *et al.*, 2008). Other jurisdictions such as Canada are considering its legalization (CCA, 2018, Rukavina, 2019). The lack of remaining treatment options, or irremediability, is one of the key requirements for psychiatric EAS in the Benelux countries (**Box 5.1**). For example, the Dutch EAS laws state that the physician must "have come to the conclusion, together with the patient, that there is no reasonable alternative in the patient's situation" (EuthanasiaCode, 2018). However, there is still ongoing discussion as to how irremediability should be defined and assessed in individual patients requesting psychiatric EAS (Gaind, 2020, Nicolini *et al.*, 2020a, Schuklenk, 2019, Sinyor and Schaffer, 2020, Smith, 2020, van Veen *et al.*, 2020). To the extent that the meaning of irremediability is partly based on scientific evidence, the ethical debate warrants further discussion of the underlying evidence grounding the commonly made arguments. One of the main issues of disagreement regards whether there is such a uniform definition of what irremediability means in psychiatry, and if so, whether it can be reliably determined and predicted (Nicolini *et al.*, 2020a).

The ethical debate about psychiatric EAS and irremediability have mainly focused on persons whose depressive disorder is treatment-resistant as a paradigm case (Blikshavn *et al.*, 2017, Broome and de Cates, 2015, Miller, 2015, Schuklenk and van de Vathorst, 2015, Steinbock, 2017). Despite various definitions, the term treatment-resistant depression (TRD) is often used in this context. However, an in-depth discussion of the underlying evidence for these ethical arguments is mostly lacking. The aim of this paper is to address this gap.

This paper is structured as follows: First, we will summarize the ethical debate about irremediability in psychiatric EAS, with a focus on the empirical claims. Next, we will review the state-of-the-art evidence for these claims, using TRD as a paradigm case. Finally, we will discuss how the findings inform the debate about irremediability in psychiatric EAS and what their policy implications are.

Box 5.1. Background information on psychiatric EAS in the Netherlands and Belgium

Legal requirements for EAS

According to the Dutch Termination of Life on Request and Assisted Suicide Act (2002), the substantive requirements are that the attending physician must: be satisfied that the patient's request is voluntary and well-considered; be satisfied that the patient's suffering is unbearable and without prospect of improvement; have come to the conclusion, together with the patient, that there is no reasonable alternative in the patient's situation; have consulted at least one other, independent physician and have exercised due medical care in terminating the patient's life (Dutch Act, 2002). According to the Belgian Act Concerning Euthanasia (2002), the physician must: come to the conviction, together with the patient, that there is no reasonable alternative in his/her condition and the request is voluntary; ascertain the continued physical or mental suffering of the patient and consult another physician about the serious and incurable nature of the disorder. If the patient is not expected to die in the near future, the following requirements apply in the Belgian Act: a second physician, a psychiatrist or a specialist in the disorder in question, needs to be consulted, and there should be at least one month between the patient's written request and the performance of euthanasia (Belgian Act, 2002).

Process and oversight systems for EAS

The Belgian Act requires that the physician consult a second physician —a psychiatrist in cases of psychiatric EAS— and requires a waiting time of at least one month for all non-terminally ill cases. While the Dutch law requires that the physician consults at least one other, independent physician, it does not specify that this be a psychiatrist for psychiatric EAS cases. However, in these cases, a psychiatric consultation is required by the Dutch Euthanasia Review Committees. Both countries have established services providing such consultants: Support and Consultation for Euthanasia in the Netherlands (SCEN) and Life End Information Forum (LEIF) in Belgium (Van Wesemael *et al.*, 2009). All EAS cases need to be reported to the Regional Euthanasia Review Committees and the Federal Control and Evaluation Commission on Euthanasia, respectively in the Netherlands and Belgium. These committees review the EAS reports to assess whether the physician who performed EAS conformed to the legal due care criteria (EuthanasiaCode, 2018, Nys, 2017).

The ethical debate about irremediability

The use of irremediability arguments in the ethical debate about psychiatric EAS can be divided into two main areas of disagreement, an empirical and a conceptual one. The first one regards the empirical claims about the existence, nature and predictability of irremediability in psychiatry. The second area, partly based on the first, discusses what the relative weight of patients' subjective versus clinician's objective assessment should be. However, both sets of arguments lack an in-depth discussion of the available evidence. This paper will focus primarily on how the state-of-the-art evidence informs the first area of disagreement, but the results of this review can serve as a basis for further analysis of the second area of dispute.

Among the empirical claims about the existence, nature and predictability of irremediability in psychiatric disorders, "the patient with treatment-resistant depression" is often invoked as a paradigm case, often in arguments in favor of psychiatric EAS (Hatherley, 2019, Player, 2018, Schuklenk and van de Vathorst, 2015, Steinbock, 2017). Authors arguing against the practice, most often clinicians, tend to appeal to general challenges within the field of psychiatry more broadly (Nicolini *et al.*, 2020a). For example, while some cite TRD as proving that truly irremediable cases do exist, this is not a disputed claim in the ethical debate: no author argues against this statement. Hence, most seem to agree that irremediability does exist in psychiatry.

For many, the crucial question is a separate one, namely whether these cases can be reliably identified. A number of authors in the debate take the position that we *cannot* make reliable predictions of chances of recovery in psychiatry, divided in three main subdivisions. First, some have argued that the field lacks a shared definition of what treatment-resistance means (Appelbaum, 2017, Blikshavn *et al.*, 2017, Broome and de Cates, 2015, Jansen *et al.*, 2019, Steinbock, 2017, Vandenberghe, 2018). Second, many have argued that clinicians cannot reliably predict long-term outcomes in psychiatry, e.g. due to limited knowledge about long-term outcomes or to the role that other, non-biological factors might play in recovery (Blikshavn *et al.*, 2017, Cowley, 2013, 2015, Jansen *et al.*, 2019, Kelly, 2017, Kelly and McLoughlin, 2002, Kim and Lemmens, 2016, Kissane and Kelly, 2000, Miller, 2015, Naudts *et al.*, 2006, Olié and Courtet, 2016, Schoevers *et al.*, 1998, Simpson, 2018, Steinbock, 2017). Third, some have argued that group level predictions of treatment-resistance or irremediability are of limited usefulness for

individual level prediction (Blikshavn *et al.*, 2017). Most of these arguments are provided by clinicians. Others, mostly non-clinicians, have argued that we *can* in fact predict irremediability, for example by using tools like the Maudsley Staging Method to determine disorder severity or group-level statistical evidence (Provencher-Renaud *et al.*, 2019, Rooney *et al.*, 2018, Tanner, 2018). The main aim of the evidence-based review in this paper will be to test these empirical claims by reviewing the state-of-the-art evidence about irremediability in psychiatry.

The ethical debate about irremediability also contains a second, more conceptual type of argument, about who should have greater decisional authority when assessing irremediability in the context of psychiatric EAS evaluations. Some state that patients can and should be able to make their own reasonable judgments about chances of recovery (Berghmans *et al.*, 2013, Cholbi, 2013, Dembo *et al.*, 2018, Dembo, 2010, Parker, 2013, Reel, 2018, Rooney *et al.*, 2018, Schuklenk and van de Vathorst, 2015, Steinbock, 2017, Tanner, 2018). While no author claims that irremediability is *purely* a clinical judgment, some argue that the determination of irremediability should not rely solely on the patient, but should also be based on the clinician's clinical judgment (Appelbaum, 2017, 2018, Cowley, 2013, Jansen *et al.*, 2019, Vandenberghe, 2018). An analysis of this set of arguments is beyond the purview of this review.

For the purpose of this paper, we will define assessments of irremediability as a predominantly objective, clinical judgment, in accordance with prevailing Dutch and Belgian professional guidelines on psychiatric EAS. For example, Dutch guidelines define irremediability as "the objective perspective of the physician" about the patient's "prospect of improvement with adequate treatment", while Belgian guidelines refer to "medical irremediability" ("*medische uitzichtloosheid*" in Dutch) (NVVP, 2018, Vandenberghe *et al.*, 2017). Our review will directly inform the debate about irremediability as well as the practice of psychiatric EAS, in a way that is relevant for further analysis of the concept of irremediability.

An evidence-based review of the empirical claims

Using TRD as a paradigm case, we will provide a review of the available evidence grounding the most prominent empirical arguments in the debate, namely whether: 1) there is (or is not) a

current uniform definition of TRD, 2) we can (or cannot) reliably predict long-term outcomes of TRD at the group-level, and 3) we can (or cannot) make individual-level predictions based on group-level predictions of long-term outcomes (**Box 5.2**).

Box 5.2. Literature search strategy and selection criteria.

We performed a literature review focusing on three research questions, namely, what is the current state-of-the-art evidence about 1) definitions and conceptualizations of TRD 2) medium to long-term naturalistic follow-up of persons with TRD 3) prediction of treatment-resistance in individual patients. For the first research question, one author (M.N) performed a broad search in PubMed with no date restriction (updated on Oct 6, 2020): ("Depressive Disorder, Treatment-Resistant" [Mesh]) with filters "Reviews" and "Systematic reviews", yielding 242 results. Reviews focusing on definitions and concepts of TRD were included; reviews about specific or novel therapeutic strategies for TRD (pharmacology, psychotherapy, neuromodulation, basic research) were excluded. A total of 11 references were included, with another 3 included through hand search, yielding a total of 14 references.

For the second research question, M.N. used the following string: ("Depressive Disorder, Treatment-Resistant" [Mesh]) AND "Follow-up"), yielding 150 references. Inclusion criteria were publications focusing on 1) unipolar treatment-resistant depression, and 2) medium to long-term outcome at follow-up. The latter focused on observational studies, excluding clinical trials where participants received adjunctive and/or experimental treatment. Medium to longer-term was defined as a period going beyond the usual period of several weeks or months as part of a clinical trial. Three publications were included, two additional references were yielded through hand search of the references, one of which was not indexed as "treatment-resistant" as it was published before the specific MeSH term was introduced in PubMed in 2012.

For the third research question, about individual prediction of treatment resistance, one author (E.J.) performed a search with a broad and inclusive MeSH term and no date restriction: "("Depressive Disorder, Treatment-Resistant"[Mesh] OR ("Depressive Disorder, Major"[Mesh] AND "Drug Resistance"[Mesh])) AND ("Algorithms"[Mesh] OR "Sensitivity and Specificity"[Mesh])". Algorithms is a broad term including subcategories such as AI, Machine Learning, Natural Language Processing, and Neural Networks, while Sensitivity and Specificity includes subcategories such as Predictive Value of Tests, Roc Curve, And Signal-to-Noise Ratio (**Appendix 5A**). Taken together, these terms narrowed the search onto papers which focused on prediction. Fifty-seven references were returned and additional

citations were hand-searched. Papers which did not report metrics on the accuracy of predictions or did not focus on treatment-resistant depression were excluded, leaving 23 studies for review.

Is there a uniform definition of treatment-resistant depression?

A total of 14 reviews were included for the first research question. All of these were published after 2012, the year in which PubMed started indexing publications about TRD under the specific MeSH term "Treatment-Resistant Depression". Of these, 71% (10 of 14) were published after 2018, indicating that this topic has been at the center of recent discussions. Two subgroups were identified: a first subgroup of articles focused on the variability of definitions of TRD and staging models and its impact on TRD research and evidence-based treatment (Brown *et al.*, 2019, Demyttenaere and Van Duppen, 2019, Gaynes *et al.*, 2020, Malhi and Byrow, 2016, McIntyre *et al.*, 2014, Ng *et al.*, 2019, Pandarakalam, 2108, Ruhé *et al.*, 2012, Sackeim *et al.*, 2019, Trevino *et al.*, 2014). A second subgroup focused on the emerging shift away from the concept of TRD in favor of the alternative notion of "difficult to treat" depression (Cosgrove *et al.*, 2020, Demyttenaere, 2019, McAllister-Williams *et al.*, 2020, Rush *et al.*, 2019).

The reviews within the first subgroup reported on the wide range of current definitions of TRD and the challenges associated with it. One recent systematic review found a total of 155 definitions for TRD among the 150 studies included, with about half (50.3%) requiring at least 2 treatment failures and only a minority (11%) including neuromodulation such as transcranial magnetic stimulation or ECT as qualifying treatment failures (Brown *et al.*, 2019). Another review found that only 20% of studies were using the most common definition of TRD of at least 2 failed treatments and systematically confirmed prior adequate dose and duration (Gaynes *et al.*, 2020). Importantly, it showed that despite the substantial morbidity of TRD, patient-oriented outcome measures focusing on functional impairment or quality of life were relatively infrequent.

Reviews within the second subgroup focused on the recent ongoing discussions about different ways to address the problem of TRD definitions and concepts. Proponents of the shift to difficult-to-treat depression call for moving away from the response and remission paradigm, towards a more holistic treatment focus that includes psychosocial functioning and quality of life

(McAllister-Williams *et al.*, 2020, Rush *et al.*, 2019). At the same time, others are skeptical about the creation of a different, more broad and inclusive label (Cosgrove *et al.*, 2020). However, proponents and skeptics alike seem to agree that current concepts of TRD have important limitations, notably the fact that it is a biologically heterogenous group and that so far it has focused mainly on psychopharmacological treatments, with only limited data on the effects of psychotherapy, neurostimulation and other emerging treatments. In conclusion, clinical evidence confirms that a single definition of TRD is lacking and discussions about the very conceptualization of TRD in clinical practice and in research are ongoing.

Can we predict group-level long-term outcomes of treatment-resistant depression?

We found that the focus on TRD and its outcomes in naturalistic settings is relatively recent, with the first systematic review of longer-term outcomes of patients with TRD published in 2009 (Fekadu *et al.*, 2009). After this review, a total of four observational studies (published between 2011 and 2014) have been published that focused on medium to long-term outcomes of TRD (**Table 5.1**).

The systematic review by Fekadu et al. is the first comprehensive review using broad inclusion criteria to incorporate follow-up studies of TRD, including studies which: 1) either defined treatment-resistance as a failure to respond to at least one antidepressant or where treatment-resistance could be inferred from the overall description, 2) were observational in nature 3) had a minimum duration of 6 months (going beyond the usual short-term follow-up as part of an acute treatment trial) 4) used defined dimensional or categorical outcomes. This review included 9 studies for a total of 1279 participants. In all but one study, patients were recruited from secondary and tertiary services. Overall, recruited patients had a chronic history of severe illness. For example, of the two studies with largest sample size, patients included had either chronic major depression or at least 4 previous episodes (Dunner *et al.*, 2006), or a history of recurrent depression in 74.7%, with mean duration of illness of 15.3 years and mean age at first episode of 25.5 (Rush *et al.*, 2006).

The largest sample size study showed a cumulative remission rate of 70% at trial endpoint of one-year follow-up (Rush *et al.*, 2006). Other studies found a "good outcome" (defined as recovery or the absence of relapse) in 38-48% (in 3 studies) and a "poor outcome" (defined as relapse or premature death) varying between 28-68% (in 3 studies). Overall, the review found that TRD is a highly relapsing condition, associated with substantial disability and mortality. However, most studies included did not primarily aim at assessing longer-term outcome of TRD: duration of follow-up was short in most studies (1-2 years). For example, the two largest sample size studies had a follow-up period of 1 and 2 years, respectively, and both studies used a very short duration to define relapse (1 week) (Dunner *et al.*, 2006, Rush *et al.*, 2006). The review leaves open the possibility that, based on longitudinal studies of affective disorders, outcome and chronicity might have been better if longer duration of follow-up had been used. Finally, only two studies reported on social outcomes and few looked at predictors of outcome.

After this review, four other studies have been published (2011-2014), the first studies to recruit participants *explicitly defined* as having TRD. All four studies were performed by the same research group in the UK. Treatment-resistance was defined as a failed response to at least 1 antidepressant, but the severity of illness was significant across studies: patients had a mean duration of illness of 16-22.2 years (Fekadu *et al.*, 2011), showed a moderately severe to severe TRD based on the Maudsley Staging Method (Fekadu *et al.*, 2012), had tried minimum one mood stabilizer in 83.5% and had received ECT in 69% (Vergunst *et al.*, 2013) or had received prolonged intensive multidisciplinary inpatient therapy with a minimum score of 16 on the 21-item Hamilton Depression Rating Scale (HDRS21) (Wooderson *et al.*, 2014). Overall, sample sizes in these studies were relatively small, ranging from 71 to 118, and two of the four studies involved the same set of participants (Fekadu *et al.*, 2012, Fekadu *et al.*, 2011).

These four studies were the first to report on longer-term outcomes (ranging from 8 months to 7 years, with an average of 3 years) in patients with TRD. The first study found that 69% achieved remission or partial remission, with outcomes at follow-up (median of 3 years) varying according to the status at discharge (Fekadu *et al.*, 2011). Remission was achieved in 70% of those discharged in remission, 50% of those discharged in partial remission and 30% of those discharged in episode. The second study found that at follow-up (ranging from 8 to 84 months), 60.2% reached full

remission, with 39.8% showing persistent depressive symptoms (Fekadu *et al.*, 2012). This was the first study to report on *predictors* of longer-term outcome in TRD patients. Higher educational achievement (hazard ratio (HR)=1.17, 95% CI 1.01–1.35; p=0.03) and strong level of social support (HR = 1.76, 95% CI 1.07– 2.89; p = 0.03) were found to be predictors of remission during follow-up. Severity of TRD was predictive for non-remission during follow-up (HR =0.82, 95% CI 0.68-0.99, p= 0.04) and poor social support was independently associated with relapse (HR=3.55, 95% CI 1.01-12.54; p= 0.05). Although not a predictor, the use of MAO-Is while inpatient was independently associated with remission at discharge after controlling for other treatments.

The third study was similar to the previous two in terms of participants and setting, with similar outcomes reported at follow-up: 60.3% were asymptomatic or at subthreshold level and 39.7% had chronic symptoms (Vergunst *et al.*, 2013). Additional outcomes involved the testing of several predictors of mean symptom severity (social support, number of prior of depressive episodes, duration of admission, life events in 12 months prior to follow-up and diagnosis). Of these, only social support was found to be a significant predictor of outcome (beta -0.356, p=0.001). The fourth study found that, with intensive multidisciplinary treatment for TRD , 66% had a good outcome and 18-34% had poor to intermediate outcome at follow-up (median of 34 months) (Wooderson *et al.*, 2014). The study showed that patients can maintain clinical improvement 3 years (mean) post-discharge following intensive multidisciplinary treatment for TRD.

The four longitudinal studies build on previous emerging evidence about long-term outcomes of TRD, as described in the first systematic review on the topic (which included the well- known large-sample STAR-D study) (Fekadu *et al.*, 2009). Although most patients in these four studies had significant severity of treatment-resistance upon entry to the study, outcomes varied, with a majority achieving remission and a substantial minority showing chronic persistent depressive symptoms. This raises a separate question, namely, whether physicians can reliably distinguish those who will recover from those who will not, on an *individual* basis. This is the focus of the next section.

Can we make individual predictions of treatment-resistance in depression?

Amongst the twenty-three studies investigating our ability to accurately predict treatment resistance, we found two main types. A first group of 13 studies focused on the question of whether an individual patient who has failed to respond to multiple past treatments will respond to the next treatment she tries. Although these studies focusing on patients with demonstrated treatment resistance are more likely to reflect clinical profiles of patients requesting psychiatric EAS, these studies were relatively new and underpowered. A second group of 10 studies focused on the question of which patients with major depression will develop treatment resistance. The literature in this area is more developed, with larger sample sizes (hundreds or thousands) and with more comprehensive sets of variables to maximize predictive ability. Taken together, these studies provide useful information about the state-of-the-art evidence on the accuracy and scope of our ability to predict treatment resistance.

Of the 13 studies in the first group focusing on patients with already demonstrated past treatment resistance (**Table 5.2A**), all but two had under fifty participants and several involved machine learning (Bailey *et al.*, 2018, 2019, Bares *et al.*, 2017, Bares *et al.*, 2015, Carrillo *et al.*, 2018, Ge *et al.*, 2017, Kautzky *et al.*, 2015, Khodayari-Rostamabad *et al.*, 2013, Micoulaud-Franchi *et al.*, 2012, Minelli *et al.*, 2016, Richieri *et al.*, 2011, Sun *et al.*, 2016, van Waarde *et al.*, 2015). Of the studies where positive and negative predictive value were reported, predictions that a patient would continue to have treatment-resistant depression were accurate 61.5% (total $N = 45$) to 100% (total $N = 21$) of the time. Overall, these studies vary in their definitions of treatment resistance at onset of the study, and are still in early experimental stages. Furthermore, the scope of their research question was narrow, namely to determine the response to a next single treatment trial, which is significantly different from the broader question of determining irremediability.

The literature on the issue of which patient with major depression might develop TRD is more extensive and has evolved to include large multi-site trials of hundreds or thousands of patients and a wide variety of predictors (**Table 5.2B**). The studies focusing on this type of predictions vary by design and study size, and can be divided in three types (in order of relevance for our

purposes): 1) pragmatic trials (i.e. reflecting real-world conditions), 2) large sampled, regimented trials involving large datasets such as the STAR*D dataset, and 3) trials using medical records.

Firstly, two studies involved uniquely pragmatic designs reflecting the conditions of available treatment for depressed patients (Chang *et al.*, 2019, Dinga *et al.*, 2018). The first study followed a group of 804 major depressive disorder (MDD) or dysthymia patients receiving any combination of pharmacological, psychotherapeutic, or no treatments (Dinga *et al.*, 2018). This study was based on data from the Netherlands Study of Depression and Anxiety, which included patients from the community as well as from specialized mental health care, covering a wide range of illness severity (Penninx *et al.*, 2008). The authors attempted to predict "chronic" depression (i.e. defined as showing no improvement from baseline after two years, versus rapid remission or gradual improvement) by latent class growth analysis (Rhebergen *et al.*, 2012). They were able to predict which patients still had chronic depression after two years with a balanced accuracy of 61%. This is the only prediction model in our review built on naturalistic study data and the study with the longest prediction endpoint, hence the most useful for determinations of long-term irremediability. However, it lacks an external validation set to test whether the model will maintain its performance outside of the data it was built with.

The second study involved a network approach to antidepressant resistance with 121 patients (Chang *et al.*, 2019). In a testing set of 13 patients with MDD, 80% of the patients who were predicted to respond to treatment did in fact respond to their prescribed antidepressants. A prediction network was designed to output modeling about the predicted effectiveness of 14 single and 91 combinations of antidepressants for every individual patient. This modeling could be used at a patient's first visit to determine which antidepressant(s) to prescribe and could be monitored during future visits to switch antidepressants as needed. The network was able to outperform baseline models both for predicting degree of antidepressant response as well as prediction of patient remission. However, the study is severely limited by a very small testing dataset ($N = 13$).

A second set of studies, involving large datasets, identified which depressed patients would not respond to their second (Kautzky *et al.*, 2017, Kautzky *et al.*, 2019, Kautzky *et al.*, 2018, Perlis, 2013) or subsequent (Nie *et al.*, 2018) trial of antidepressants. All of them involved STAR*D or

GRSD (Group for the Study of Resistant Depression) datasets. Each included not only large patient samples for model development (ranging from 400 to 2,454 patients) but also the largest external validation samples (ranging from 80 to about 460 patients). However, despite large sample sizes, the predictive accuracy of the models during validation were variable. For predictions that a patient would improve, the models were correct from 39% (*N* = 225) to 81.9% (*N* = 314) of the time. For predictions that a patient would not respond to a second or subsequent antidepressant, the models' accuracy ranged from 66.5% (*N* = 80) to 92% (*N* = 225).

A third set of studies used patient records to predict treatment resistance (Cepeda *et al.*, 2018, Perlis *et al.*, 2012). Cepeda et al (2018) used insurance claims of 22,057 patients, to predict which patients would go on to receive ECT, deep brain stimulation, or vagus nerve stimulation after trying at least one antidepressant in the past year. The authors found that their algorithmically-derived decision-tree rule performed more accurately in internal validation than any of the five decision rules defined by expert psychiatrists (*F-1* = 0.44 compared to *F-1*'s = 0.39 - 0.42) and held up in an external validation samples totaling 14,845 patients from alternate insurance databases (*AUC*s = .78-.79). Similarly, Perlis (2012) used natural language processing of 5,198 patient records to develop a model predicting whether patients were depressed on every given visit following an initial antidepressant prescription. The authors were able to accurately classify individual visits as depressed (vs well), with a positive predictive value of 78%. Next, patients were classified as treatment resistant if they had a majority of predicted-depressed visits despite 2 antidepressant trials in the past year. Based on this definition, agreement between the model's predictions of treatment resistance and the opinion of a board of expert clinicians was 76.4%. Although both of these studies have promising implications, such as the potential to screen risk for treatment resistance without data collection, they take an unconventional approach to defining treatment resistant depression.

In sum, there is a growing body of evidence assessing the accuracy of predictions about treatment resistance. Of the 23 studies reviewed, over half made predictions about whether patients who have already failed two or more antidepressant trials will respond to their next treatment. Ten additional studies focusing on whether depressed patients will develop treatment resistance, typically defined by failing to respond to two or more antidepressant trials. Across studies,

predictive accuracy across a range of metrics fluctuated between 40% and 100%, but these studies were still considered preliminary.

Discussion of the main findings

The notion of irremediability continues to be central in the ethical debate about psychiatric EAS. A main area of disagreement regards what exactly we mean by irremediability, whether we can reliably predict group-level long-term outcomes in TRD, and whether we can make individual-level predictions based on group-level predictions. A thorough clinical-ethical discussion can only begin with a clear understanding of the evidence underlying such claims. Using TRD as the paradigm case, this paper provides an evidence-based review of these three central empirical claims in the ethical debate around irremediability.

The first claim pertains to whether there a single, uniform definition of TRD exists. Depression can be a serious, severe, and chronic condition. Although the term TRD has gained wide use, the term started to be used (primarily for research purposes) relatively recently, with PubMed starting to index papers as focusing on TRD only since 2012. There is an ongoing debate about its definition and conceptualization. Currently, over 150 definitions exist (Brown *et al.*, 2019), with important implications for the way research about TRD is being performed (e.g. making it more difficult to replicate results) and more generally, for the status of knowledge about the condition. Furthermore, there is ongoing discussion about what the appropriate outcome measures for TRD should be, with quality of life outcome measures being infrequently used. Some have proposed to reconceptualize TRD as difficult-to-treat, with a greater focus on psychosocial functioning and quality of life (McAllister-Williams *et al.*, 2020, Rush *et al.*, 2019). Hence, we found ample evidence that definitions and conceptualizations of TRD are ongoing.

The second claim related to whether long-term outcomes of TRD can be predicted on a group-level. We found that, to date, there are only four naturalistic studies focusing on medium to long-term outcomes in patients who are explicitly defined as having TRD (Fekadu *et al.*, 2012, Fekadu *et al.*, 2011, Vergunst *et al.*, 2013, Wooderson *et al.*, 2014). They show that a significant minority of patients have chronic and difficult to treat clinical course. Hence, from a clinical perspective,

this is a reality. However, it is also notable that even when well-characterized as chronic and treatment resistant at the onset of the studies, and after years of community treatment, a majority seemed to significantly improve. The findings are in line with as those of the STAR*D study, where patients achieved about 70% remission rate, despite a high number of previous episodes and length of episodes when entering the study. Furthermore, these studies offer useful insights into predictors of outcome in TRD. This will need further investigation through larger sample studies, including to further investigate to what extent predictors in TRD overlap with those in depression more broadly (De Carlo *et al.*, 2016).

Although these five studies are the first to use well-operationalized outcomes in patients with TRD, they have a number of limitations. First, the studies included in the systematic review were heterogeneous, making it difficult to generalize findings. Second, the four data-based studies all stem from the same research group, with relatively small sample sizes and showing overlap between various studies in terms of participants. The small sample sizes form a challenge for the feasibility of testing predictors of outcome. Third, even though participants were well-characterized as having TRD, the way TRD was defined remains heterogenous, limited the usefulness of the findings. Fourth, TRD remains primarily defined in terms of failed psychopharmacological treatments, only rarely including psychotherapeutic treatment and excluding other emerging treatments such as neuromodulation. Finally, knowledge about predictors and naturalistic population outcomes of TRD, while useful and necessary, is of limited use for the question of individual prognosis prediction.

The third subdomain focused on the evidence about individual-level predictions of treatment-resistance, i.e. how accurately clinicians can determine, on a case by case basis, who will and who will not achieve remission or recovery in practice. This was divided in the question of which patient with past treatment resistance will respond to a next treatment, and which patient with major depression will develop treatment resistance. Our review found that individual prediction studies, even the larger studies focusing on treatment response amongst patients with depression, are cautiously accurate in development but are not yet ready to be applied in practice. However, prediction psychiatry is an exponentially growing field, subject to rapid change.

Studies focusing specifically on prediction of treatment response for patients who have already failed multiple treatments are relatively limited in size and scope: they mostly utilize small sample sizes, involve only on specific treatments (e.g. transcranial magnetic stimulation, psilocybin), and focus only on particular, experimentally-relevant predictors (e.g., seizure quality). Although these studies suggest that predictions of treatment response can be accurate up to 100% of the time (though with a very small sample study of 21), most authors describe them as preliminary studies. More work is required before this can be applied and validated in clinical practice.

Even among the larger studies of patients with depression, where accuracy gets as high as 82%, available knowledge is limited to predict improvement at the end of treatment. Although this provides useful preliminary information, it does not allow for predictions of sustained remission or lifelong recovery. Of the 23 reviewed studies, only one involved long-term prediction (Dinga *et al.*, 2018). The model developed by Dinga et al, which predicted who would continue to have chronic depression after two years of any or no treatments, found that about half (47%) of the chronically depressed patients were correctly predicted to be so.

The studies reviewed have a number of limitations. First, most models in our review only predict whether or not patients will respond to a particular treatment. Second, as exemplified by Chang et al's (2019) network approach, the most useful predictions will not only involve whether a patient's depression will improve, but which of many treatments, if any, will work best for the individual patient. Although work of this nature was not included in our review, treatment selection for depression is a growing area of literature (Cohen and DeRubeis, 2018). Third, besides the question of clinical application, there are important remaining methodological concerns regarding accuracy. Methodological flaws in precision psychiatry may result in the wrongful inflation of accuracy estimates, which may further preclude immediate implementation into practice. Researchers are beginning to discuss common errors in machine learning research and to publish guidelines on best practices (Hosseini *et al.*, 2020, Jacobucci *et al.*, 2020, Poldrack *et al.*, 2020). These include, for example, using sample sizes greater than several hundred participants and avoiding leave-one-out cross-validation. Notably, many of the studies reviewed were not able to follow these practices. Those which did, such as Nie et al., 2018, tended to have lower performance metrics, providing some evidence for the idea that studies not following best practices likely provide overestimations

of accuracy. Indeed, much of the excitement about clinical applications of prediction models is paralleled by recognition that more work must be done first (DeRubeis, 2019, Gillan and Whelan, 2017, Perna *et al.*, 2018). Therefore, many of the reviewed models, including those with the highest accuracies, such as a positive predictive value of 100% in a study of 21 patients (Micoulaud-Franchi *et al.*, 2012), might need to be cautiously interpreted as overestimations of our true predictive ability.

Implications for the ethical debate about irremediability

The results of this review directly inform the ethical debate about irremediability, defined as partly a clinical or scientific concept. First, evidence supports the claim that there is a lack of consensus in the scientific literature on how to define TRD, which has implications for both the debate and the practice of psychiatric EAS. The term TRD remains a working definition used primarily for research purposes and its very definition is still being debated. This does not deny the existence of patients who are treatment-resistant; rather, it underscores the importance of this clinical reality. But it suggests that, given the heterogeneity of definitions, invoking the construct of TRD in the debate about psychiatric EAS might not be as informative as often assumed. In fact, it might not reflect clinical practice, where TRD as defined in research is rarely used (Brown *et al.*, 2019). This is partly reflected in psychiatric EAS guidelines, which do not refer to "treatment-resistance" in their specific guidance on irremediability, but instead focus on general terms used in clinical practice, such as diagnosis, treatment options and prognosis (NVVP, 2018).

Second, the available evidence supports the claim that the knowledge about long-term outcomes of TRD on a group-level is relatively limited. This provides support for the general claim that there is great prognostic uncertainty in psychiatry (Blikshavn *et al.*, 2017, Cowley, 2013, 2015, Jansen *et al.*, 2019, Kelly, 2017, Kelly and McLoughlin, 2002, Kim and Lemmens, 2016, Kissane and Kelly, 2000, Miller, 2015, Naudts *et al.*, 2006, Olié and Courtet, 2016, Schoevers *et al.*, 1998, Simpson, 2018, Steinbock, 2017). Furthermore, the fact that a majority of patients will enter remission, even those defined as having severe illness using prevailing staging methods, shows that a diagnosis of TRD is not sufficient to establish irremediability. Therefore, there is little support for the claim that available staging methods for TRD or group-level statistical evidence

can be used in order to reliably predict chances of recovery (Provencher-Renaud *et al.*, 2019, Rooney *et al.*, 2018, Tanner, 2018).

Available knowledge about predictors of long-term outcomes in TRD provides preliminary support for the claim that both non-biological and biological factors affect chances of recovery in psychiatric disorders. For example, social support was repeatedly found to be a predictor of long-term outcome in TRD (Fekadu *et al.*, 2012, Vergunst *et al.*, 2013). The role of social support is especially relevant for the debate about psychiatric EAS. Empirical studies suggest that social isolation plays a role in patients' requests: social isolation was reported in over half of psychiatric EAS cases in the Netherlands in one study (Kim *et al.*, 2016), and described as one of the reasons for requesting psychiatric EAS in a Belgian qualitative study (Verhofstadt *et al.*, 2017). Similarly, whether certain biological treatments can predict recovery needs further study. One example is the use of MAO-inhibitors, which was not a predictor but appeared independently associated with remission in TRD patients (Fekadu *et al.*, 2012). MAO-inhibitors have been shown to be used only in a small minority of depressed persons who received psychiatric EAS (Kim *et al.*, 2016). Hence, while further research with larger-scale samples is needed to establish the range of predictors of long-term outcome in TRD, available evidence provides support for the claim that recovery in psychiatry, more so than in other medical field, depends on *both* biological and non-biological factors.

Third, our review points to the fact that clinicians may not have sufficient information to make a reliable determination of *individual* chances of recovery. There is a growing amount of empirical evidence relevant to the question of prediction of individual treatment response in patients with demonstrated treatment resistance, which more likely reflect situations of patients requesting psychiatric EAS. Models in development show an ability to make accurate predictions of treatment resistance up to 61-100% of the time. However, these models are narrowly construed to a specific context and have methodological limitations. They often vary in definitions of treatment response and resistance, and in representativeness of treatment options. Among studies predicting treatment resistance in patients with major depression, the model which came closest to reflecting real-life conditions accurately predicted who would continue to have chronic depression (after two years of any or no treatments) in only 47% of the cases (Dinga *et al.*, 2018). A one in two chance of

accurate prediction is not likely to be a comfortable margin for clinicians assessing irremediability in the context of psychiatric EAS evaluations. As such, we conclude that irremediability cannot yet be *accurately* predicted in clinical practice on an individual basis. Absent reliable prediction tools, assessments of irremediability will continue to include lower levels of certainty than often assumed in the ethical debate about irremediability. However, it is clear that this issue is likely to see exponential progress in the next few years.

As the field advances, two important policy considerations will continue to be salient. A key issue is the question of decision under uncertainty. Developments in the field prediction psychiatry will likely help quantifying the uncertainty involved in predictions of irremediability. But a separate policy question is what might be an acceptable threshold for certainty in the context of (psychiatric) EAS. Some have argued that certainty cannot be a *conditio sine qua non* for regulatory action, for if it where the case, "no further regulatory action can be taken on any subject" (Schuklenk, 2019). Others have pointed to the fact that policies must be "responsive to the significant practical uncertainties" and "able to reliably identify individual cases in which [*EAS*] would be ethically justified" (Jansen *et al.*, 2019, Steinbock, 2017). For individual prediction of treatment resistance in psychiatry, there are no agreed-upon standards regarding what level of accuracy is required for clinical application. On a statistical level, accuracies above or around 80% tend to be described as high-performing, although there are no clear-cut thresholds. Of the twelve models in our review which report overall accuracy, algorithmic predictions were accurate at determining treatment outcomes anywhere from 70% to 93% of the time. Whether an *ideal* of 7% to 30% inaccuracy would be an acceptable or too high a margin of error in the context of psychiatric EAS, remains an important policy question.

Finally, there is the question of how clinician and algorithmic predictions relate to and inform each other. For example, a meta-analysis comparing clinical versus statistical prediction of human behavior found that statistical predictions were often more accurate than clinicians' judgments (Grove *et al.*, 2000). However, no recent studies have compared clinician and algorithmic predictions of treatment outcome for depression. Parallel work on predicting recovery from alcohol use disorder shows that based on overall accuracy alone, the best-performing machine learning model was more accurate (70%) than clinical predictions (56%) (Symons *et al.*, 2020). However,

clinicians were much better at identifying patients who will respond to treatment (70%) than the best-performing machine learning approach (17%). This suggests that the relationship between clinician and algorithmic predictions is likely complex, warranting further study.

Strengths and Limitations

This review aimed at filling the evidence gaps in the ethical debate around irremediability, so as to inform the debate and provide a basis for further discussion. There are a number of limitations to this evidence-based review. First, while this is not a systematic review, this review aims at providing a thorough evidence-based review of the scientific literature around a topic of ethical importance. Second, we chose TRD as a paradigm case and focused on the literature on the topic as this has been the paradigm case within the ethical debate on the topic. The results remain limited to TRD and do not extend to other psychiatric disorders, such as schizophrenia or bipolar disorder. However, the same type of review can be applied to these disorders, for example using available evidence for prediction algorithms in these cases (Alonso *et al.*, 2018). Finally, in practice, virtually all psychiatric EAS cases involve substantial psychiatric comorbidity, limiting the usefulness of the findings of this study in real-life cases. However, the focus on TRD in this paper is primarily to inform further evidence-based and ethically sound discussion about the concept of irremediability in the debate about psychiatric EAS.

Conclusion

Irremediability remains at the center of debates about the practice of EAS for psychiatric disorders. The main area of disagreement regards the question of whether clinicians can reliably predict chances of recovery, or irremediability, in the field of psychiatry. Using TRD as a paradigm case, this paper provides a thorough review of the current evidence undergirding some of the main arguments about the issue of irremediability in psychiatry. This, in turn, can further inform clinical, ethical and policy debates about the practice.

Table 5.1. Overview of medium- to longer-term outcome of TRD.

First systematic review of 9 studies on medium- to longer-term outcome of TRD.

Reference	Patient characteristics	Setting	N	Outcome	FU period	Predictors	Strengths
Fekadu 2009	TRD defined as failed response to min.1 antidepressant; *and* one of following: HRS-D25 >15, MDD in various stages of resistance; HRSD >18; referred for ECT; residual symptoms or chronic depression	Mostly from secondary/ tertiary services; 1 study from outpatient setting	1279	Good outcome (recovery or absence of relapse) in 38%-48% (3 studies) Poor outcome varied between 28% and 68% (3 studies)	ranging between 1-10 years, but short in most studies (1-2y)	For good outcome & recovery - initial responsiveness to lithium - absence history of admission - shorter duration of illness & less severe illness during FU For poor outcome & readmission -prior history of treatment with lithium -presence of delusions & agitation	First systematic review of short- and longer-term outcomes studies of (heterogeneously defined) TRD

Follow-up studies of longer-term outcome in patients with TRD.

Reference	Patient characteristics	Setting	N	Outcome	FU period	Predictors	Strengths
Fekadu 2011	TRD defined as failed response to min. 1 antidepressant trial; Other: duration of illness ranging between 16-22.2y	Patients discharged from specialized in-patient treatment unit	118	Measures used: LIFE chart, PSR 69% remission or partial remission < 40% full remission at any one follow-up point in time At FU: Remission in 70% of those discharged in remission	median of 3 years	For long-term outcome: Posttreatment clinical status at discharge (defined by PSR score) AOR 3.1 95%CI 1.91-5.07	First report on longer-term outcome as a function of baseline end of treatment clinical status in explicitly defined TRD patients

				50% of those discharged in partial remission 30% of those discharged in episode			
Fekadu 2012	TRD defined using the MSM with mean severity of 10.1 (moderate to severe on average); Other: 65% ECT; mean number of prior AD 5.9; 60% history of suicide attempt (unipolar =77; bipolar = 27; secondary TRD = 14)	Patients discharged from specialized in-patient treatment unit	118	Main measures used: LIFE chart, PSR At discharge Remission 33.9% Partial remission 30.5% Persistent depressive symptoms 35.6% At FU 48.3% recovery (defined as in remission for min.6 mo) 11.9% remission (defined as asymptomatic for min. 1mo) 39.8% persistent depressive symptoms	ranging from 8 to 84 mo; mean 39mo mean HRSD 20.5	For remission during FU -Educational achievement HR=1.17, 95% CI 1.01–1.35; p=0.03 -Level of social support HR = 1.76, 95% CI 1.07–2.89; p = 0.03 For non-remission during FU -Severity of TRD defined by MSM HR=0.77, 95%CI 0.68-0.99, p= 0.04	First report on predictors of longer-term outcome and in explicitly defined TRD patients
Vergunst 2013	TRD defined as: failed response to min. 1 antidepressant trial; Other: min. 1 mood stabilizer in 96 (83.5%); prior ECT in 69% (unipolar =84; bipolar=31)	TAU after discharge from specialist tertiary unit	115	Main measures used: LIFE chart and PSR At FU: 60.3% asymptomatic or subthreshold level; 39.7% chronic symptoms (15.8% mild; 13.9% moderate; 10%severe)	ranging from 1-7 years (median 36mo)	For mean symptom severity during FU -Social support (beta -0.356, p=0.001)	Reports analyses predicting symptom severity fluctuations and symptom severity from range of social and clinical variables.
Wooder-son 2014	TRD defined as commensurate with entry criteria for	specialist multi-disciplinary treatment	71	Main measure used: HDSR-21 score of 10 or less; CGI At FU	median 34mo;	None reported.	First study looking at long-term outcome in TRD subgroups in terms of diagnosis, HDRS21

	STAR*D (unipolar n=51; bipolar n=20)			Good outcome 66% Intermed/poor outcome 34% Responders 56% Remission 51%	IQR 19-52		factors, pattern of response to treatment and psychosis history. Identifies *possible* predictors of response.

Abbreviations used in Table 5.1 (Alphabetical)

AOR: Adjusted Odds Ratio (odds ratio that controls for other predictor variables)
AD: Antidepressant
CI: Confidence Interval
ECT: Electroconvulsive therapy
FU: Follow-up
HRSD: Hamilton Rating Scale for Depression – 25 items/18 items
HR: Hazard Ratio
IQR: Interquartile Range
LIFE: Longitudinal Interval Follow-up Chart
MDD: Major Depressive Disorder
MSM: Maudsley Staging Method
PSR: Psychiatric Status Rating Scale
STAR*D: Sequenced Treatment Alternatives to Relieve Depression Study
TAU: Treatment as Usual
TRD: Treatment-Resistant Depression

Table 5.2 Individual Prediction of Treatment-Resistance in Depression								
Citation	**Purpose**	**Sample (Trial)**	**Disorder at Inclusion**	**Intervention**	**Trying to predict...**	**Definition of TRD (non-response or resistance)**	**Prediction endpoint**	**Predictors / features**
Section A Predicting TRD Patients' Response to Additional Treatment								
Bailey et. al (2018)	Among treatment resistant patients, use baseline EEG and clinical measures to predict who will respond to TMS.	39 TRD patients	TRD as defined by Stage 2 of Thase and Rush classification; HAM-D >20	5-8 weeks of rTMS	responders (metrics recalculated)	< 50% reduction in HAM-D	at the end of treatment	16 EEG, 3 mood, and 6 behavioral features
Bailey et. al (2019)	Among treatment resistant patients, use baseline EEG and clinical measures to predict who will respond to TMS.	42 TRD patients	TRD as defined by Stage 2 of Thase and Rush classification; HAM-D >20	5-8 weeks of rTMS	responders (metrics recalculated)	< 50% reduction in HAM-D	at the end of treatment	53 EEG variables and 1 clinical (MADRS)
Bares et al. (2017)	Among treatment resistant patients, use one EEG and one clinical measure to predict response to SSRI treatment.	38 TRD patients	"at least" Stage I according to Thase and Rush; MADRS >= 25 and CGI >= 4.	6-weeks of SSRI treatment	responders (metrics recalculated)	at least 50% reduction in MADRS score	At the end of treatment	Combination of reduction in MADRS >= 20% at week 2 and EEG decrease of cordance at week 1 compared to baseline
Bares et al. (2014)	Among treatment resistant patients, use one EEG and two clinical measures to predict response to SSRI treatment.	87 TRD patients	"at least" Stage I according to Thase and Rush; MADRS >= 25 and CGI >= 4.	at least 4-weeks of antidepressant treatment	responders (metrics recalculated)	at least 50% reduction in MADRS score	At the end of treatment	Combination of reduction in MADRS >=20% at week 1, reduction in MADRS >= 20% at week 2, and EEG reduction of cordance value at week 1 compared to baseline

Carrillo et al. (2018)	Among treatment resistant patients, use average negative and positive words during initial interview to predict who will respond to psilocybin.	17 TRD patients	resistance as defined by >= 17 on HAM-D and failure at least 2 AD trials	2 doses of psilocybin	responders (metrics recalculated)	<50% reduction in QIDS	5 weeks post-treatment	2 features: average positivity and average negativity during baseline autobiographical memory test
Ge et al. (2017)	Among treatment resistant patients, use fMRI data from one brain region to predict response to rTMS.	18 TRD patients	failure to achieve clinical response to an adequate dose of an antidepressant based on an Antidepressant Treatment History Form (ATHF) score of >= 3 OR unable to tolerate at least 2 separate trails of antidepressants of inadequate dose and duration (ATHF 1 or 2); AND HDRS=17 >= 18	4-6 weeks of rTMS	responders (metrics recalculated)	at least 50% improvement in HRSD	At the end of treatment	Dorsal anterior cingulate cortex in the salience network from fMRI
Kautzky et al. (2015)	Among depressed patients, use combination of SNPs and clinical variables to predict treatment resistance after 1 antidepressant trial.	225 MDD patients (from GSRD)	MDD, diagnosed according to DSM-IV criteria	At least 1 antidepressant trial (most received more than one)	responders (metrics recalculated)	HAM-D > 17 after at least one AD trial	at the end of treatment	3 SNPs and 1 clinical variable (melacholia)
Khodayari-Rostamabad et al. (2013)	Among treatment resistant patients, use baseline EEG	22 TRD patients	TRD as defined by failure to respond to at	6 week SSRI treatment	responders (metrics recalculated)	< 30% improvement	at the end of treatment	pre-treatment EGG measures

	measures to predict who will respond to an additional antidepressant trial.		least 2 previous antidepressant trials and HAM-D >= 18			between pre/post HAM-D		
Micoulaud-Franchi et al. (2012)	Among treatment resistant depressed and bipolar patients, use one EEG measure to predict response to rTMS.	21 treatment resistant MDD and BD patients	non-response to pharmacological treatment of depression using a minimum of 2 distinctly different classes of antidepressant medications	20 rTMS sessions over 4 weeks	responders (metrics recalculated)	at least 50% reduction of baseline BDI scores	At the end of treatment	EEG pre-treatment alpha band power in the right
Minelli et al. (2016)	Among treatment resistant patients, use seizure quality to predict response to ECT.	45 TRD patients	failure to respond to at least 2 antidepressant trials of different classes AND to an adequate trial of a tricylic (TCA) (Stage III of Thase and Rush)	ECT therapy 3 times per week until considered complete by judgment of treating physicians	responders (metrics recalculated)	at least 50% reduction in MADRS score	1 month after the end of treatment	seizure quality of the 4th and 6th ECT sessions, as rated by 2 doubled blinded independent psychiatrists
Richieri et al. (2011)	Among treatment resistant patients, use composite score from brain SPECT to predict response to rTMS.	33 TRD patients	non-response to pharmacological treatment of depression using a minimum of 2 distinctly different classes of antidepressant medications	20 rTMS sessions over 4 weeks	responders (metrics recalculated)	at least 50% reduction in baseline BDI scores	At the end of treatment	composite score for whole-brain voxel-based regional cerebral blood flow from baseline brain SPECT
Sun et al. (2016)	Among treatment resistant patients, predict remission of suicidal ideation	27 TRD patients	"quantified with the antidepressant treatment history	24 sessions of magnetic seizure therapy or until remission of	Remission of suicidal ideation	SSI score of 0	At the end of treatment	baseline TMS-EEG measures 1 week before MST - measures of cortical inhibition

	using EEG measures in the prefrontal cortex to predict response to MST.		form". they do not specify in the methods if a cut-off score was used. in the introduction, they define TRD as inability to respond to 2 or more separate trials of antidepressants	depressive symptoms* *(defined as HRSD <= 10 and 60% reduction in symptoms for at least 2 days)	(metrics recalculated)			(e.g., N100 and LICI) in the frontal cortex
Van Waarde et al. (2015)	Among severely depressed and/or treatment resistant patients, use baseline fMRI measures to predict response to ECT treatment.	45 severe MDD / TRD patients	"severe and/or treatment-resistant depression as diagnosed by at least 2 independent experienced psychiatrists" according to the DSM-IV; does not explain how treatment resistance is defined	2 weekly ECT sessions for up to 10 weeks	responders (metrics recalculated)	MADRS > 10	at the end of treatment	resting-state networks from MRI and fMRI
Section B Predicting Depressed Patients' Development of TRD								
Dinga et al. (2018)	Among MDD patients, use mood, behavioral, and EEG measures to predict who enters rapid remission vs. gradual improvement vs. chronic depression (TRD).	804 MDD or dysthymia patients (from NESDA)	MDD or dysthymia patients	any pharmacological or psychotherapeutic treatment or no treatment	TRD	3 classification groups formed by latent class growth analysis, where TRD is the 'chronic' group (and the other two groups are: rapid remission; gradual improvement)	2 years after treatment	81 clinical variables, personality dimensions, demographic variables, and biological variables (BMI, inflammatory markers, metabolic syndrome variables, vitamin D levels, and more)

Chang et al. (2019)	Among depressed patients, predict which of 14 antidepressants (or 91 combinations of antidepressants) will decrease a patient's depression scores the most.	121 MDD patients 13 MDD patients for external validation	MDD, not specified	At least 1 antidepressant trial	responders (metrics recalculated)	< 50% reduction in HAM-D	at the end of treatment	127 demographic features, 20 neuroimaging biomarkers, 20 genetic variants, and 20 DNA methylation features chosen from elastic net feature selection. (Antidepressant info is accounted for in one of the other neural network layers)
Cepeda et al. (2018)	Using medical claims records of depressed patients, use clinical features of drug utilization to predict which patients will later receive ECT, DBS, or VNS (as a proxy for TRD).	22,057 patients in the CCAE insurance claims database 14,845 patients in two other insurance claims databases for external validation	MDD or other depression diagnosis	at least 1 antidepressant in the past year	TRD (proxy)	patients with a procedure code on inpatient or outpatient medical claims record for electroconvulsive therapy (ECT), deep brain stimulation (DBS), or vagus nerve stimulation (VNS)	up to 1 year after initial AD prescription	10 features involving drug utilization and number of therapy sessions extracted from claims
Perlis et al. (2012)	Using medical records and billing codes of depressed patients, predict whether a patient was depressed or well during each visit, and then classify whether they are treatment-resistant based on the ratio of well to	5,198 MDD patients from out-patient psychiatry medical records and billing codes	at least one billing code with diagnosis as MDD	at least 1 antidepressant trial within a 12-month period	TRD	machine learning was used to classify each visit as either depressed or well or intermediate. those classified with 'TRD' had to meet the following criteria: 2+ depressed visits within 12	Up to one year after first AD prescription	34 features from natural language processing of medical records and billing codes

	depressed visits during antidepressant trials over a 1-year period.					months following an initial AD prescription, no well visits, a majority of all visits classified as depressed, and exposure to at least 2 ADs during this period		
Kautzky et al. (2017)	Among depressed patients, use combination of clinical, sociodemographic, and psychosocial variables to predict treatment resistance after 2 antidepressant trials	400 MDD patients (from GSRD) 80 MDD patients for external validation	MDD, diagnosed according to DSM-IV criteria	2 antidepressant trials	TRD	HDRS >= 17 after at least 2 AD trials	at the end of treatment	48 clinical features
Kautzky et al. (2018)	Among depressed patients, use 47 clinical and sociodemographic features to predict whether patients will respond to their second antidepressant treatment for the current depressive episode.	552 MDD patients (from GRSD) 119 MDD patients for external validation	MDD, diagnosed according to DSM-IV criteria	2 antidepressant trials	TRD	< 50% reduction in MADRS and MADRS >= 22	at the end of treatment	15 clinical features (the top 15 predictors taken from the initial 47)
Kautzky et al. (2019)	Among depressed patients, use 16 clinical features to predict who will respond to their second antidepressant treatment for the current depressive episode.	602 MDD patients (from GRSD's TRD-III) 314 MDD patients for external validation	MDD, diagnosed according to DSM-IV criteria	2 antidepressant trials	TRD	TRD-III: <50% reduction in MADRS and MADRS and MADRS >= 22 TRD-I: HAM-D >= 16	at the end of treatment	16 clinical features

		(from GRSD's TRD-I)						
Perlis (2013)	Among depressed patients, use clinical variables to predict who will respond after 1-2 antidepressant trials versus who will not respond after 2.	2,094 MDD patients (from STAR*D) 461 MDD patients for external validation	MDD, diagnosed according to DSM-IV criteria	sequential treatment levels beginning with citalopram for 12 weeks, then moving to randomized next level if still not remitted.	TRD	QIDS-SR > 5	at the end of treatment	15 clinical variables chosen from initial 48 during feature selection
Nie et al. (2018)	Among depressed patients, use nearly 700 diverse features to predict who will not respond after 2 antidepressant treatment trials.	2,454 MDD patients (from STAR*D) 225 MDD patients for external validation (from RIS-INT-93)	STAR-D: met DSM-IV criteria for MDD RIS-INT-93: met DSM-IV criteria for MDD and "had history of resistance to therapy with AD medication"	STAR*D: went through 4 levels of treatment options, for up to 12 weeks each RIS-INT-93 cohort: treated with citalopram for up to 6 weeks	TRD	STAR*D: > 5 on QIDS-C or QIDS-SR RIS-INT-93: > 7 on HAM-D	at end of treatment	began with 700 clinical features; for validation, used set of 22 overlapping features

Table 5.2 (Cont.)												
Citation	**Methodology**	**Form of validation**	**Flipped? (*)**	**AUC**	**Sens.**	**Spec.**	**PPV**	**NPV**	**Acc.**	**Bal. Acc**	**F1**	**Other**
Section A Predicting TRD Patients' Response to Additional Treatment												
Bailey et. al (2018)	Linear support vector machine (SVM) classifier with 5-fold cross-validation	cross-validation	Yes		0.92*	0.91*				0.91	0.93	10 responders of 39, prevalence = .2564
Bailey et. al (2019)	Linear support vector machine (SVM) classifier with 5-fold cross-validation	cross-validation	Yes		0.89*	0.84*				0.866		12 responders of 42, prevalence = .2857
Bares et al. (2017)	Inferential statistics with ROC analysis	None	Yes	0.92			0.71*	0.95*	0.84			Number needed to diagnosis = 1.4
Bares et al. (2014)	Inferential statistics with ROC analysis	None	Yes	0.91			.8*	.85*	0.83			Number needed to diagnosis = 1.53
Carrillo et al. (2018)	Gaussian Naive Bayes classifier with 7-fold cross-validation	cross-validation	Yes					0.75*	0.85			
Ge et al. (2017)	Inferential statistics with ROC analysis	None	Yes	0.939	.82*	1*			0.939			11 responders of 18, prevalence = .6111

Kautzky et al. (2015)	Random forest classifier with 10-fold cross-validation	cross-validation	Yes			0.25*		0.5*				
Khodayari-Rostamabad et al. (2013)	Mixture of Factor Analysis classifier with leave-n-subjects-out (LnO) cross-validation	cross-validation	Yes		0.8093*	0.9486*			0.879			7 responders of 22, prevalence = .3182
Micoulaud-Franchi et al. (2012)	Inferential statistics with ROC analysis	None	Yes	0.815	0.66*	1*	1*	.8*				Cut point = 1.49 mu-V
Minelli et al. (2016)	Inferential statistics with ROC analysis	None	Yes	0.74	0.688*	0.897*	0.615*	0.828*				Cut point = medium quality seizure
Richieri et al. (2011)	Inferential statistics with ROC analysis	None	Yes	0.89	.73*	.94*	.92*	.81*				
Sun et al. (2016)	Inferential statistics with ROC analysis	None	Yes	0.9	.89*	.9*			0.89			Authors reported remission rate as 53%.
Van Waarde et al. (2015)	Support vector machine (SVM) classifiers with leave-one-per-group-out cross-validation	cross-validation	Yes		0.85*	.84*		0.88*				
Section B Predicting Depressed Patients' Development of TRD												
Dinga et al. (2018)	Multinomial generalization of penalized elastic net logistic regression classifiers with 10-fold cross-validation	cross-validation	No	0.66	0.47					0.61		

Chang et al. (2019)	Neural network architecture with a patient layer, AD prescription layer, and prediction layer.	external validation	Yes		.875*	.8*		0.8*	0.846		0.8	
Cepeda et al. (2018)	Decision-tree classifiers with 80-20 train-test split, no cross-validation	external validation	No	0.79								
Perlis et al. (2012)	Logistic regression classifier with adaptive LASSO procedure and 3-fold cross-validation	cross-validation	No						0.764			
Kautzky et al. (2017)	Random forest classifier with 10-fold cross-validation	external validation	No		0.633	0.8	0.665	0.784	0.737			
Kautzky et al. (2018)	Random forest classifier with 10-fold cross-validation	external validation	No		0.803	0.603	0.819	0.603	0.706			0.396
Kautzky et al. (2019)	Elastic net logistic regression classifier with 10-fold cross-validation	external validation	No		0.857	0.875	0.793	0.917	0.869			0.124

Perlis (2013)	Of 4 machine learning approaches using 10-fold cross-validation, logistic regression classifier performed the best	external validation	No	0.719	0.259	0.911						
Nie et al. (2018)	Of 5 machine learning approaches using 10-fold cross-validation, random forest classifier performed the best	external validation	No	0.86	0.92	0.36	0.92	0.39	0.73			

(*) Sensitivity and specificity and PPV and NPV were recalculated for some studies so that all metrics reflect prediction of TRD as the positive class.

Abbreviations used in Table 5.2

Psychiatric Diagnosis
BP: Bipolar disorder
MDD: Major Depressive Disorder
TRD: Treatment-resistant depression

Diagnostic tools and markers
EEG: Electroencephalogram
fMRI: Functional Magnetic Resonance Imaging
MST: Magnetic Seizure Therapy
SNP: Single nucleotide polymorphisms
SPECT: Single-photon emission computerized tomography

Rating Scales
ATHF: Antidepressant Treatment History Form
BDI: Beck Depression Inventory
CGI: Clinical Global Impression Rating Scale
HAM-D: Hamilton Depression Ration Scale

MADRS: Montgomery-Asberg Depression Rating Scale
QIDS: Quick Inventory of Depression Symptomatology

Treatment types
AD: Antidepressant
DBS: Deep Brain Stimulation
rTMS: Repetitive Transcranial Magnetic Stimulation
SSRI: Selective Serotonin Reuptake Inhibitor
TCA: Tricyclic antidepressant
VNS: Vagus Nerve Stimulation therapy

Datasets
GSRD: Group for the Study of Resistant Depression
NESDA: Netherlands Study of Depression and Anxiety study
RIS-INT-93: protocol number of a large dataset available via Yoda Project
STAR*D: Sequenced Treatment Alternatives to Relieve Depression Study
TRD-I/III: Datasets based on GSRD data

Methodology
Acc.: Accuracy
AUC: Area under the ROC curve
Bal. Acc.: Balanced Accuracy
F1: Weighted average of Precision and Recall (evaluation measure in machine learning)
NVP: Negative Predictive Value
PPV: Positive Predictive Value
ROC analysis: Receiver-Operating Characteristic Analysis (tool for evaluating accuracy of a statistical model
SVM: Support Vector Machine

Appendix 5A. Individual Prediction using Machine Learning

Section A: Some frequently used terms and their explanation

Artificial Intelligence	Broadly defined, the use of advanced computer programming and mathematics to design automated forms of human intelligence.
Algorithm	Used to refer to the product(s) of any mathematical model produced by a form of artificial intelligence. For example, 'algorithm' can be synonymous with 'machine learning model'.
Machine Learning	An umbrella term for many types of artificial intelligence wherein computers identify complex patterns in data and use these patterns to 'learn' how to steadily improve a task without human intervention.
Supervised Machine Learning	A form of machine learning where the pattern identified in the model (e.g., the 'learning') is confirmed or denied by corresponding data, allowing for estimates of model's performance or accuracy. See Section B below.
Natural Language Processing	A form of artificial intelligence wherein computers are trained to identify and understand human language.
Neural Networks	A form of advanced machine learning, also called 'deep learning', built to mimic the structure and complexity of the human brain. Neural networks involve several layers of modeling and are therefore considered more complex than most forms of supervised machine learning.
Sensitivity	See Section C below
Specificity	See Section C below
Predictive Value	See Section C below
ROC Curve	A plot of the true positive rate against the false positive rate of a classification (e.g., disease vs no disease). Generally used to compare the accuracy of a diagnostic tool or test.
Signal-to-Noise Ratio	There is always a chance that datasets will include some patterns or correlations which occur by random chance alone (e.g., do not represent a real pattern or correlation). These random errors are considered "noise" in the dataset. Additionally, we typically hope that datasets will include some patterns or correlations that reflect real-world differences. These correlations are considered to be a 'signal' of the effect in the dataset. Most statistical analyses, including machine learning, aim to determine to what extent patterns or correlations in the dataset reflect true real-world patterns ('signal') versus random error ('noise'). A higher signal-to-noise ratio denotes a more significant effect.

Adapted from "What Is artificial intelligence?" *Built In* (2019). Retrieved from https://builtin.com/artificial-intelligence.

Section B: How Supervised Machine Learning Works

Study Population	Ideally, collect data from hundreds of patients.
Feature Selection	Decide what predictors (or 'features') should be entered into the prediction model. Typically begins with variables previously identified in clinical literature as having predictive value, but also includes other predictors which have not been well-investigated. Some authors select a set of features and build a model using all of them. Others start with a large set of features (sometimes 100's), and use a data-driven approach for feature selection, which is an iterative process where the best (most predictive) features are chosen while other (non-predictive) features are dropped from the model.
Training the Model	A subset of data is used to 'train' the algorithm. Data are labelled -- the dataset includes whether or not each patient responded to the treatment ('outcomes'). There are many mathematical techniques for this 'training' (e.g., support vector machine, k-nearest neighbors, random forest), but most utilize some form of error calculation to identify patterns in the data that predict outcomes.
Testing the Model	A subset of the data is used to 'test' the algorithm. Data are unlabeled -- e.g., the dataset includes all the predictors for each patient, but does not include whether or not the patient responded to the treatment. The algorithm makes predictions as to whether or not the patient will respond to treatment based off of what it learned in the training. Then, the model's predictions of outcomes are compared to the true outcomes of each patient. Measures of model accuracy comparing predictions to actual outcomes can then be computed.
Cross-Validation	An iterative process where the subsets of data used for training and testing are changed over different subsections ('folds') of data until every subset of data has been used for testing at least once. Cross-validation provides some insurance against overfitting.
External validation	After the model is trained and tested, there may still be some concern about overfitting. Many researchers recommend that, even after cross-validation, it is important to validate the model's performance on a set of data it has never been trained on before. Sometimes, this external validation is a set of data that was collected in tandem with the other data, but was 'held-out' of training (and of cross-validation). Other times, the validation set is a completely different dataset collected on a different protocol or by different researchers. Sometimes, researchers only choose external validation datasets that cover all the same measures; other times, researchers choose external validation datasets which overlap with only some measures, in which case the model can only take those measures into account (potentially harming performance).

Section C: Confusion Matrix Defining Model Metrics.

		Actual		
		Has TRD	**Does NOT Have TRD**	
Predicted	**Predicted to Have TRD**	**True Positive** Predicted to be treatment-resistant when they are treatment resistant.	**False Positive** Predicted to be treatment-resistant when they actually will improve with treatment.	**Positive Predictive Value** Percent of individuals predicted to be treatment-resistant who truly will not improve with treatment.
	Predicted to NOT Have TRD	**False Negative** Predicted to improve when they actually are treatment resistant.	**True Negative** Predicted to improve when they truly will improve.	**Negative Predictive Value** Percent of individuals predicted to improve with treatment who truly will improve with treatment.
		Sensitivity / Recall Percent of individuals with treatment resistance who are correctly predicted to be treatment resistant.	**Specificity** Percent of individuals who will respond to treatment who are correctly predicted to respond to treatment.	

Chapter 6: Psychiatric EAS, Suicide and The Role of Gender

Nicolini M.E., Gastmans C., Kim S.Y.H. Psychiatric Euthanasia, Suicide and the Role of Gender. *British Journal of Psychiatry* (Forthcoming)

Abstract

The preponderance of women among psychiatric EAS cases has received virtually no discussion. In this analysis, we argue that two seemingly unrelated features of psychiatric EAS are actually deeply related. Understanding how they are related can elucidate both phenomena, and frame the debate over psychiatric EAS in a new and illuminating way. The first feature is the gender gap in psychiatric EAS: patients are predominantly women. The second feature has been a key debate point in the controversy over psychiatric EAS, namely, its tension with suicide prevention. In this paper, we argue that the gender gap disproves current explanations for the difference between psychiatric EAS and suicide, which assume that suicide is an impulsive action while an EAS request is not. Using contemporary suicide theory, we find that the gender gap in psychiatric EAS can be explained in terms of gender differences in suicide capability, a concept used in the literature to refer to the extent to which a person uses effective means for suicide. This suggests the relation between suicide and psychiatric EAS is based on capability, not impulsivity. If this is true, patient profiles might be more similar in terms of risk for suicidal behavior than often assumed, raising several implications for the practice of psychiatric EAS and public policy.

Introduction

Euthanasia and/or medically assisted suicide (EAS) when primarily based on a psychiatric disorder (psychiatric EAS), as permitted in some European countries such as Belgium and the Netherlands, remains controversial (Griffith *et al.*, 2008, Jones *et al.*, 2017). In those countries, EAS is permitted if a patient suffers unbearably and irremediably due to a medical (including psychiatric) condition (**Box 6.1**). In psychiatric EAS, women account for the majority (69-77%) of cases (Kim *et al.*, 2016, Thienpont *et al.*, 2015, van Veen *et al.*, 2019). While this is one of the most consistent findings in EAS research, the gender gap and its meaning have received virtually no discussion.

In this paper, we discuss how understanding this gender gap can inform a key dispute in the debate about psychiatric EAS, namely its tension with suicide prevention. One way to address this tension is to argue that psychiatric EAS and suicide are different phenomena, characterizing suicide as an impulsive act of violent self-destruction, and EAS as a planned and well-considered act (Creighton *et al.*, 2017). However, it is unclear whether this distinction is empirically founded. We will examine whether and how the gender gap can inform this question in an evidence-based manner.

In the following sections, we first critically examine current accounts of the difference between psychiatric EAS and suicide. Next, we turn to ideation-to-action theories of suicide, arguing that, when combined with the gender gap in psychiatric EAS, such theories support the hypothesis that there are no relevant differences between persons requesting psychiatric EAS and persons attempting suicide. Finally, we outline the implications of this finding for the practice of psychiatric EAS. We argue that the pool of potential psychiatric EAS requestors and the associated risk for error might be higher than previously assumed, and explain how current guidance might contribute to this risk. We conclude by drawing some implications for public health policy.

Box 6.1. Background information on psychiatric EAS in the Netherlands and Belgium

Legal requirements for EAS

According to the Dutch Termination of Life on Request and Assisted Suicide Act (2002), the substantive requirements are that the attending physician must be satisfied that the patient's request is voluntary and

well-considered and that the patient's suffering is unbearable and without prospect of improvement and must have come to the conclusion, together with the patient, that there is no reasonable alternative in the patient's situation (Dutch Act, 2002). The Belgian Act Concerning Euthanasia (2002) has similar albeit differently formulated key requirements: the physician must come to the conviction, together with the patient, that the request be voluntary, that the disorder be serious and incurable and must ascertain that the physical or mental suffering of the patient cannot be alleviated (Belgian Act, 2002).

Process and oversight systems for EAS

The Belgian Act requires that the physician consult a second physician —a psychiatrist in cases of psychiatric EAS— and requires a waiting time of at least one month for all non-terminally ill cases. While the Dutch law requires that the physician consults at least one other, independent physician, it does not specify that this be a psychiatrist for psychiatric EAS cases. However, in these cases, a psychiatric consultation is required by the Dutch Euthanasia Review Committees. Both countries have established services providing such consultants: Support and Consultation for Euthanasia in the Netherlands (SCEN) and Life End Information Forum (LEIF) in Belgium (Van Wesemael *et al.*, 2009). All EAS cases need to be reported to the Regional Euthanasia Review Committees and the Federal Control and Evaluation Commission on Euthanasia, respectively in the Netherlands and Belgium. These committees review the EAS reports to assess whether the physician who performed EAS conformed to the legal due care criteria (EuthanasiaCode, 2018, Nys, 2017).

Understanding the gender gap in psychiatric EAS

Current explanations for the difference between psychiatric EAS and suicide

Current explanations for the difference between psychiatric EAS and suicide describe different phenomena, with emphasis on the alleged different role of impulsive action in both cases (Creighton *et al.*, 2017, den Hartogh, 2016, Kim *et al.*, 2018). The American Association for Suicidology states that suicide and EAS, *including* psychiatric EAS, are quite distinct, involving different patient characteristics. They characterize suicide as associated with violent self-destruction, isolation, loss of meaning, ambivalence and psychological pain. On the other hand, they describe persons requesting EAS as, instead, engaging in a planned act of self-preservation,

experiencing intensified emotional bonds with loved ones (Creighton *et al.*, 2017). Others have also characterized suicide as a quasi-impulsive, violent and lonely act, to be distinguished from EAS, seen as a carefully executed, non-violent plan in dialogue with others (den Hartogh, 2016). Current explanations for the different gender distributions in suicide and psychiatric EAS are grounded in this same distinction: suicides are violent and impulsive (hence involving more men), whereas psychiatric EAS is planned and controlled (hence involving more women) (van Veen *et al.*, 2019).

Such contrasting portrayals of persons who die by suicide versus those who die by EAS as fundamentally different rely on unfounded assumptions (Kim *et al.*, 2018). Their key reliance on impulsivity can be challenged, as the role of impulsive action in suicide has been overstated and only very little suicidal behavior (lethal or non-lethal) occurs without planning (Anestis *et al.*, 2014, Klonsky *et al.*, 2016, O'Connor and Nock, 2014). In fact, impulsive attempts are associated with *lower* psychopathology (Anestis *et al.*, 2014), while individuals who are at particularly high risk for suicide (i.e. those with depression, substance use, a history of childhood sexual abuse) are less likely to engage in impulsive attempts. Impulsive action is neither necessary nor sufficient for suicide and cannot explain the difference between suicide and psychiatric EAS, nor its different gender distributions.

We should therefore reexamine this empirically unsupported assumption. For this purpose, we will consider the usefulness of ideation-to-action theories, which focus on the suicidal *process* from suicidal ideation to behavior (Klonsky *et al.*, 2016, O'Connor and Nock, 2014, Van Orden *et al.*, 2010). This framework has received considerable clinical and research attention (O'Connor and Nock, 2014, Turecki *et al.*, 2019). Rather than emphasizing the role of suicide risk factors, it focuses on the concept of suicide "capability", which determines the transition from suicidal ideation to (lethal and non-lethal) suicidal behavior. Within this framework, "capability" includes practical factors (knowledge of and access to highly lethal means) and psychological factors (fearlessness of death, pain tolerance), both of which can be acquired over time (Franklin *et al.*, 2011, Klonsky *et al.*, 2016, O'Connor and Nock, 2014, Schrijvers *et al.*, 2012, Turecki *et al.*, 2019, Van Orden *et al.*, 2010). In the following sections, we analyze the gender distributions in suicide

and psychiatric EAS and examine the potential role for capability as an alternative, empirically-grounded explanation for the relation between suicide and psychiatric EAS.

Capability, gender and suicide

The difference between the gender distribution in suicide and that in suicide attempts is well-known and is referred to as the suicide "gender paradox" (Canetto and Sakinofsky, 1998, Schrijvers *et al.*, 2012). The most consistently cited explanation for this paradox is the gender difference in methods chosen: women choose less violent and lethal methods than men (Conner *et al.*, 2019, Hawton, 2000, Schrijvers *et al.*, 2012). For example, men tend to use highly lethal methods such as hanging or fire-arms, while women often choose less lethal, self-poisoning methods. Indeed, even when same methods are used, lethality is higher among men (Mergl *et al.*, 2015). Assuming availability and knowledge of highly lethal methods is equal for both genders, the gender differences in method selection and implementation is accounted for primarily by the psychological component of capability (Van Orden *et al.*, 2010). Indeed, research suggests that differences in capability among suicide attempters is what accounts for why more men die by suicide than women (O'Connor and Nock, 2014).

The choice for low lethality methods may indicate lower suicide capability, especially as it relates to the psychological aspects, since these methods may be perceived as involving less physical pain and relatively less frightening (Klonsky *et al.*, 2018, Nock *et al.*, 2010, O'Connor and Nock, 2014). Furthermore, the robust finding that women show a higher number of non-lethal attempts prior to a lethal attempt is consistent with the claim that through repeated attempts, women gradually increase their capability and the lethality of their attempts (Anestis *et al.*, 2014, Isometsa and Lonnqvist, 1998, Schrijvers *et al.*, 2012, Van Orden *et al.*, 2010). However, it is important to note that socio-cultural beliefs and attitudes towards suicidal behavior play a role in explaining capability and gender differences in suicide (Canetto, 2008, Turecki *et al.*, 2019). For example, in Western countries, non-lethal suicidal behavior is considered more socially acceptable for women than for men, but this may be different in non-Western countries (Dahlen and Canetto, 2002). High female suicide rates in countries like China (Turecki and Brent, 2016), show that women's so-

called low capability for suicide in Western countries may vary depending on the context and does not necessarily constitute an intrinsic female characteristic.

Capability, gender and psychiatric EAS

The above framework suggests a natural explanation of the gender gap in psychiatric EAS, if we abandon the distinction between psychiatric EAS and suicide based on impulsivity. And, given the concept of capability invoked by ideation-to-action theories of suicide, there is good reason to do so. EAS is a painless and highly lethal method of death, that is professionally and socially approved in countries where it is legal. The important psychological components of capability involve the ability to face death and to enact something painful to one's own body (Franklin *et al.*, 2011, Van Orden *et al.*, 2010). These barriers are removed when someone receives EAS, as it does not involve pain or violence. Furthermore, EAS is equally accessible and culturally acceptable to both genders, given the similar rates of end-of-life EAS in men and women (Canetto, 2019, Dierickx *et al.*, 2016, Downar *et al.*, 2020, Hedberg and New, 2017, Onwuteaka-Philipsen *et al.*, 2017, Steck *et al.*, 2016).

This finding is analogous to the well-known case in suicidology of high female suicide rates in rural China. This is attributed to men and women's equal access to readily available, non-violent yet highly lethal pesticides, as opposed to the less toxic analgesics and psychotropic medications commonly ingested in high-income countries (Schrijvers *et al.*, 2012, Turecki and Brent, 2016, Turecki *et al.*, 2019, WHO, 2019). The case of rural China shows that mortality significantly increases when persons who want to die, but with otherwise low suicide capability, have access to non-violent, lethal methods.

Given that the different gender distributions in suicide and psychiatric EAS are primarily accounted for by differences in capability, we should expect similar gender ratios between suicide *attempters* (as opposed to completers) and persons receiving psychiatric EAS. And this is what we find. Men are 2 to 3 times as likely to die by suicide than women in most countries, including in the Netherlands, while women are about twice as likely (2.1:1) to *attempt* suicide (Bernal *et al.*, 2007, Kim *et al.*, 2016, Thienpont *et al.*, 2015, Turecki *et al.*, 2019, WHO, 2019). The women:

men ratio in psychiatric EAS (2.3:1) is virtually identical to that of suicide attempters, not completers. This suggests that the relation between suicide and psychiatric EAS is based on capability, not on the problematic concept of impulsivity. This means that patient profiles are similar in terms of risk for suicidal behavior, but with varying levels of capability. Persons with low capability who might not die if they attempt suicide, can achieve death if they use EAS instead.

Discussion

Whether psychiatric EAS conflicts with the duty to prevent suicide remains a topic of debate. One way to address this tension is to distinguish between suicide and (psychiatric) EAS, by characterizing suicide as an impulsive, typically violent action, and EAS as planned and well-considered (Creighton *et al.*, 2017). However, our analysis shows that this distinction is not empirically-grounded and does not in itself refute the claim that psychiatric EAS is in tension with suicide prevention. Ideation-to-action explanations of suicide, focusing on the suicidal *process*, suggest that the distinction is not as straightforward as some have argued. The notion of capability that they invoke proves that the "gender paradox" in suicide is closely related to the gender gap in psychiatric EAS: women resort to psychiatric EAS as a form of suicide of which they are "capable". And, as we have shown, the numbers undergird this analysis. Persons requesting psychiatric EAS are similar to those attempting suicide, a finding corroborated by data from the practice of psychiatric EAS in the Netherlands and Belgium (Kim *et al.*, 2016, Kim *et al.*, 2018, Nicolini *et al.*, 2020b, Verhofstadt *et al.*, 2017). In suicide terms, the use of EAS turns attempters with low capability into completers. This raises several, so far underexplored, implications for the practice of psychiatric EAS and public policy.

First, it suggests that the number of persons engaging in suicidal behavior, *both* non-lethal and lethal (i.e. suicide attempters and completers) could provide an approximation of the pool size of potential psychiatric EAS requestors. For example, in a country like Belgium with 11 million inhabitants -and with notoriously high suicide rates- the region of Flanders counts 3 suicides and an estimated average of 28 suicide attempts per day (Vancayseele *et al.*, 2018). This amounts to 1,095 suicides and over 10,000 suicide attempts per year – 9 attempts for every suicide. It is reasonable to assume that a significant proportion of these persons might consider psychiatric EAS

at some point during their suicidal process, as psychiatric EAS becomes better known as an option. Hence, the pool of potential requestors is large, perhaps more so than previously assumed, with a vast majority of attempters. For some, providing a more humane alternative to persons who would otherwise die by suicide is the aim of psychiatric EAS (Berghmans *et al.*, 2013, Dembo *et al.*, 2018, Truyts, 2020). For example, psychiatrist Lieve Thienpont, one of the three physicians acquitted in the Belgian Tine Nys court trial, stated that "We have 3 to 4 suicides per day in Flanders, 90% of whom suffer mentally. What can we do to shift this suicidal thought to a request for euthanasia?" (Truyts, 2020). However, this view does not take into account that such a shift would not be limited to suicide completers only.

Second, a large pool of potential requestors that mostly consists of suicide attempters raises the issue of an increased opportunity for error, i.e. the risk for available deaths. The risk for error, or "false positives", is a known area of dispute in the debate about psychiatric EAS (Nicolini *et al.*, 2020a). Scholars disagree on whether it should count as an argument against psychiatric EAS or merely as grounds for caution. Regardless of where one stands, the dispute has so far mainly referred to potential errors in assessing the irremediability of the person's psychiatric condition, their unbearable suffering or their decision-making capacity. The findings of our analysis point to a different *type* of risk, namely the one associated with not detecting suicidal behavior that could respond to treatment. The question is particularly salient for subgroups with low suicide capability and a more protracted suicide process, like women or younger adults (Schrijvers *et al.*, 2012, Turecki *et al.*, 2019), as the choice of psychiatric EAS over traditional means of suicide results in substantial increase in mortality. That is, the difference between expected mortality rates through suicide versus through EAS is highest in these subgroups and "false positives" will, on average, come at a higher cost for each individual.

One way to address this conundrum is by establishing clear guidance for clinicians, to identify those whose requests for psychiatric EAS stem from suicidal ideation and behavior that could respond to treatment. Currently, guidelines are silent on whether suicidal ideation and behavior should play a role in how "irremediability" is defined, potentially exacerbating the risk for error. In fact, they define the criterion exclusively in terms of treatment options for the underlying psychiatric condition (Berghmans *et al.*, 2009, Vandenberghe *et al.*, 2017). This may be due to the

assumption that treating a psychiatric condition will also improve associated suicidal behavior. However, this assumption is mistaken. Treatments targeting a psychiatric condition do not necessarily reduce suicidal thoughts or behavior (O'Connor and Nock, 2014). Furthermore, while established evidence-based treatments for suicidal behavior exist, including pharmacological and psychological treatment, only about 60% of people with suicidal ideation and behavior receive treatment (O'Connor and Nock, 2014). This raises important questions about the extent of unmet needs among persons at risk for suicide who request psychiatric EAS.

For example, psychological treatments such as dialectical behavior therapy (DBT) for borderline personality disorder or cognitive therapy for recent suicide attempters have proven effective (O'Connor and Nock, 2014, Turecki *et al.*, 2019). However, in a recent analysis, we found that these interventions are rare among persons receiving psychiatric EAS: cognitive therapies were reported in 14% and DBT in none of the 74 included personality-related disorder cases, while 47% had attempted suicide once and 36% multiple times prior to their request (Nicolini *et al.*, 2020b). To reduce the risk that a psychiatric EAS request stems from suicidal behavior, potentially leading to false positives, further discussion is needed about the role for established suicidal behavior treatments in current guidance defining irremediability. This is particularly relevant going forward, since psychiatric evaluations are often performed by non-psychiatrists, as both the Netherlands and Belgium continue to face difficulties recruiting psychiatrists willing to be actively involved in these evaluations (Huisman, 2017, Truyts, 2020, van de Wier, 2019).

Finally, the similarities between persons at risk for suicide and those requesting psychiatric EAS calls for further attention to population-wide suicide risk factors that may apply to psychiatric EAS. For example, the effect of media reporting on imitation behavior is a risk factor targeted in key population-level suicide prevention strategies (Turecki *et al.*, 2019). While the regulation of media reporting does not apply to (psychiatric) EAS (Miller, 2019), similar patterns of imitation could be expected in persons who consider requesting psychiatric EAS. To assume that the same patterns do not apply is only tenable if the clinical profiles are distinct, but not if they appear similar. Yet patients' perceptions and attitudes towards others' deaths by psychiatric EAS remains an open empirical question.

In addition, the overlap between suicide and psychiatric EAS calls for further research to better characterize persons who request psychiatric EAS. Given that the majority of suicide attempters are women, particular attention should be paid to women's reasons for requesting psychiatric EAS. This includes further research into why women are more prone to psychiatric disorders in the first place, why some request psychiatric EAS while others do not, and why some proceed with their request once it is granted, while others withdraw. But, if some of the reasons why women request psychiatric EAS also include known actionable *suicide* risk factors, gendered or societal, this raises additional issues, warranting attention in the context of psychiatric EAS and public policy. For example, gender-based violence, affecting 35% of women worldwide, is a gendered environmental suicide risk factor that is common among persons requesting psychiatric EAS (Nicolini *et al.*, 2020b, Oram *et al.*, 2017, Verhofstadt *et al.*, 2017) and an important public health issue for which prevention and management remains suboptimal (Oram *et al.*, 2017). Hence, the findings of this analysis raise policy implications that go far beyond the boundaries of psychiatry.

Conclusion

Despite being empirically well-established, the gender gap in psychiatric EAS has been underexplored so far. An analysis of its meaning using the ideation-to-action suicide theories shows that the gender gap provides key evidence that persons requesting psychiatric EAS are more similar to persons engaging in suicidal behavior than often assumed. This raises important implications for the practice of psychiatric EAS and public health policy.

Chapter 7: General Discussion

The practice of psychiatric EAS has been debated for over 25 years, after the famous Chabot case in 1994 led to de facto legalization of the practice in 1997 in the Netherlands (Griffith *et al.*, 2008, Thomasma *et al.*, 1998). The Dutch and Belgian laws on Euthanasia and Assisted Suicide enacted five years later in 2002 did not contain restrictions regarding the *type* of medical condition needed to be eligible for EAS, hence also permitting psychiatric EAS. But while this practice has been in place for over 20 years ago now, cases have started to increase slowly but steadily since 2011, with the first empirical studies emerging around 2015. Hence, our understanding of the practice is still in its early stages.

This project had three main aims. First, providing patient-level insights into salient clinical and ethical challenges associated with psychiatric EAS evaluations, particularly as they relate to the assessment of irremediability and unbearable suffering (Chapter 2). Second, to provide a comprehensive and minimally-biased overview of the ethical arguments used in the international debate about psychiatric EAS (Chapter 3). This is important for policy-making in countries debating extending of their EAS laws to non-terminal, psychiatric disorders. But it is also relevant for countries, like the Benelux, where the practice is already permitted but remains contentious, by helping clinicians determine and shaping their own ethical position in the debate. Third, based on the results of the first two parts, this project aimed at analyzing in more detail three subareas of ethical disagreement that were considered most salient and directly relevant for both policy and clinical practice (Chapters 4-6).

In this concluding chapter, I first provide a summary of the main findings of this dissertation and describe in what ways these results are novel. Next, I formulate a set of recommendations for the practice of psychiatric EAS and the ethical debate about the issue. Finally, I discuss methodological considerations, potential limitations and avenues for future research.

Summary of the Main Findings

In Chapter 2, I discussed the empirical findings of a mixed-methods study focusing on personality disorders. The study focused on personality disorders (with borderline personality disorder as the most common type) for a number of reasons. First, because they are, together with depression, the most prevalent condition among psychiatric EAS cases (Kim *et al.*, 2016, Thienpont *et al.*, 2015). Second, because their chronicity, prevalence, and impact on outcomes of co-morbid Axis I psychiatric disorders are considered significant. Third, because some of the characteristic features, such as feelings of helplessness and hopelessness may be difficult to distinguish from feelings of intolerable and hopeless suffering (which are eligibility criteria for EAS). And finally, because the complex interpersonal interactions they invoke, including with clinicians, can make the EAS evaluation processes potentially challenging.

The study found that a majority of cases were women, virtually all with significant psychiatric comorbidities. One of the most notable findings was that, despite the usually long courses of disease, in over a fourth of cases (28%) first line treatment, i.e. psychotherapy, had not been tried. For example, among the known standard evidence-based treatments for cluster B personality disorders (which includes borderline personality disorder), ranging from cognitive-behavioral to psychodynamic treatments, dialectical behavior therapy was not mentioned in any of the cases, schema-focused treatment had been tried once and mentalization-based treatment was considered but not tried in one case. Another key finding was that clinicians used the word "palpable" (Dutch: *invoelbaar*), term adopted by the RTE's guidance on how to assess unbearable suffering, almost exclusively when evaluating patients with personality disorders. This may indicate the presence of (counter)transference during these evaluations, which so far had only been mentioned as a theoretical possibility (Berghmans *et al.*, 2009). This suggests that clinicians could be uniquely emotionally affected by the suffering of patients with personality disorders seeking EAS, in ways that may not always be clear or conscious of them. The larger ethical question this raises is that the RTE's guidance on the matter, which uses the term with the intention to guide clinicians in their assessment of any patient requesting EAS, not just when based on psychiatric disorders (Swildens-Rozendaal and van Wersch, 2015), may actually lead physicians to operate with certain potentially misleading patient-physician interpersonal dynamics.

Finally, the study pointed to some emerging themes, such as the specific subset of patients with both psychiatric and physical comorbidities. These patients, even with their more chronic and severe clinical histories, were overall *less* likely to receive specialized psychiatric care, more likely to be referred to End-of-life clinic and more likely to be evaluated by a non-psychiatrist. Some of the possible explanations are that physicians assessing these patients, general practitioners in particular, are more inclined to use a 'medical model' of disorder rather than focusing on psychological treatments. While this was only a subset of cases, this offers important potential insights into the evaluations of patients with complex needs and suggests greater level of expertise might be needed. In closing, this study was the first to focus on the highly prevalent cases of persons with personality disorders. It suggests that both patient- and clinician-related factors play a role in the evaluations in ways that might not have been appreciated sufficiently before.

In Chapter 3, through the use of a systematic review of reasons, I describe the state of the ethical debate involving the reasons in favor and against extending EAS based on a terminal condition to EAS based on a psychiatric condition. This was the first systematic review of ethical literature on the topic. The specific type of bioethics literature review used aims at providing a comprehensive overview of the debate around a contentious ethical issue, which in turn can inform argument-based policy-making. The review showed that arguments invoking the parity of mental and physical suffering, and mental and physical disorders, figured prominently in the debate. These "parity" or "non-discrimination" arguments state that "If EAS is permitted for X, then it should be permitted for Y, given that there are no relevant differences between X and Y". This type of argument was often invoked by authors with a non-clinical background and from countries where access to EAS is limited to terminal illness, such as the USA, Australia or Canada. However, the policy implications of extending EAS to EAS based on a psychiatric condition were discussed more broadly by clinicians and non-clinicians. One common denominator of the implications is the greater "risk for error" in psychiatric EAS evaluations, compared to evaluations for terminal, physical disorders. The risk for error refers to the greater uncertainty (i.e. risk of inaccurate judgments) involved when assessing decision-making capacity, unbearable suffering and irremediability in psychiatry. This suggests that a mere focus on non-discrimination as an ideal concept might not be sufficient for appropriate policy-making and safe practice.

Seven other domains were found, which related to decisional capacity, irremediability, goals of medicine and psychiatry, consequences for mental health care, psychiatric EAS and suicide, self-determination and authenticity, and psychiatric EAS and refusal of life-sustaining treatment. Overall, the debate was in its early stages, with most articles written after 2013. While there was an even engagement between clinicians and non-clinicians, most contributions from clinicians consisted of commentary-type pieces, as opposed to well-developed articles with full-fledged argumentation. Notably, direct engagement between authors was relatively rare.

Chapter 4 explores the non-discrimination argument in more detail, in particular its nature, structure and limits. First, it notes that the nature of the argument is conditional, as noted earlier. This means that it starts with the premise that some form of EAS should be permitted: the argument can only work if that is taken to be true. What it often fails to note, however, is that, if parity exists and the conclusion turns out not to be permissible, then the starting position itself is not permissible (here, EAS for terminal illness). Second, a deconstruction of the argument shows that it relies heavily on the assumption that suffering is the justification for EAS in terminal, physical illness, which itself can be debated. Third, it mainly argues that there are no relevant differences between mental and physical suffering, with lesser focus on the question of difference between mental and physical disorders. Finally, the chapter concludes by describing the fourth part of the argument, which is the assumption that the consequences of permitting psychiatric EAS are not worrisome enough to counter its merits. Proponents of the parity argument assume that an idealized conceptual argument can ground policy-making. But the range of known and unknown consequences of permitting psychiatric EAS is broad, ranging from consequences for patients, for mental health care and for society at large.

Chapter 5 focuses on the concept of irremediability as it is used in the ethical debate about the practice of psychiatric EAS. It provides an evidence-based review of some of the assumptions, which can in turn further inform the debate and policy-making. The chapter focuses on three most debated issues: a) whether there is a single, shared definition of treatment-resistance, b) whether clinicians can reliably predict long-term outcomes and chances of recovery in psychiatry, and c) whether we can make individual-level predictions based on group-level predictions. The aim of the review is to empirically test each of these three claims, using treatment-resistant depression as

a paradigm case. The results showed that there is ample empirical evidence for the first claim: major discussions are ongoing about the definitions and conceptualizations of treatment-resistant depression. Second, relatively little is known about long-term outcomes (i.e. months and years) of treatment-resistant depression and its predictors. Finally, although the literature on individual prediction of treatment resistance is promising and growing exponentially, studies focusing specifically on persons with TRD have small sample sizes and vary in design. Studies using larger samples are not designed to answer predictions in patients with TRD. Hence, evidence suggests that individual prediction models are still largely in preliminary phases and are not yet ready to be applied in practice with a high degree of accuracy.

These results inform ethical debate about irremediability in the following ways. First, it suggests that invoking the "TRD patient" in the debate might not be as helpful as often assumed: there is no uniform definition of TRD, and the concept is used primarily for research, not for clinical purposes. Second, available knowledge about predictors of long-term outcomes in TRD point to the fact that a mere diagnosis of TRD, or high severity score on a staging method, is not sufficient to establish irremediability, since outcomes vary even among patients with chronic histories. Furthermore, it provides preliminary support for the claim that both non-biological and biological factors affect chances of recovery in psychiatric disorders, particularly the role of social support. Finally, since irremediability cannot yet be *accurately* predicted in clinical practice on an individual basis, assessments of irremediability will continue to include lower levels of certainty than often assumed in the ethical debate about irremediability.

Chapter 6 brings together two seemingly unrelated, but deeply related, issues related to psychiatric EAS. One the one hand, the consistent finding that women are overrepresented among psychiatric EAS cases. On the other hand, there is a major conceptual tension between psychiatric EAS and suicide prevention. This chapter describes how the gender gap can inform the tension between psychiatric EAS and suicide, in ways that provide insights for the practice. Contemporary suicide theories were used to analyze the gender gap, which suggest that persons requesting psychiatric EAS and persons attempting suicide show similar clinical profiles. If this is correct, this raises a number of policy implications. First, this means that the pool of psychiatric EAS is potentially large, and could be expected to grow significantly in the future, as the practice becomes more well-

known. Second, a large pool of requestors means that there might be a greater risk of false positives. While the debate has so far mainly referred to potential errors in assessing irremediability of the person's psychiatric condition, unbearable suffering and decision-making capacity, this analysis points to the risk of not assessing, or not detecting, suicidal ideation or behavior that could respond to treatment. Third, this finding has implications for how we define irremediability. Currently, guidelines are silent on whether suicidal ideation and behavior should play a role in how "irremediability" is defined. Defining the criterion exclusively in terms of treatment options for the underlying psychiatric condition risks overseeing unmet needs among persons at risk for suicide who request psychiatric EAS. Finally, the finding points to inconsistencies between how we treat patients requesting psychiatric EAS and suicidal patients. This includes, but is not limited to, the prevention strategies in place to prevent suicide and the population-wide suicide factors, some of which could be shared with persons requesting psychiatric EAS.

Recommendations

The General Discussion of this dissertation will be discussed in the form of recommendations. These are to be regarded as general considerations based on the empirical and conceptual findings of this project. This includes recommendations for (1) current guidance and procedural safeguards in the practice of psychiatric EAS, focusing on the Netherlands and Belgium, (2) the international ethical debate about psychiatric EAS, and (3) public health policy (**Table 7.1**).

Table 7.1. Overview of Recommendations

General	Specific	No.
(1) Improving guidance and procedural safeguards in psychiatric EAS practice	Establishing boundaries between suffering and irremediability	1
	Refining clinical interpretations of irremediability	2
	Including greater expertise over longer time periods	3
(2) Broadening the ethical debate about psychiatric EAS	Including all stakeholders involved	4
	Addressing shortcomings of the non-discrimination argument	5
	Incorporating ongoing discussions about personal recovery	6
	Integrating empirical evidence in ethical argumentation	7
(3) Focusing on the tension between psychiatric EAS and suicide prevention	Examining psychiatric EAS through the lens of suicide	8
	Clarifying conceptually inconsistent notions of informed consent	9
	Investigating how suicide risk factors apply to psychiatric EAS	10

Improving guidance and procedural safeguards in psychiatric EAS practice

Recommendation No. 1: Establishing boundaries between suffering and irremediability

In some countries where psychiatric EAS is permitted, such as in Belgium and the Netherlands, unbearable suffering and irremediability requirements are two necessary conditions. Hence, adequate boundaries between irremediability and unbearable suffering are important. However, while in theory these are two different conditions, in practice they are often considered together. Part of this is because of the way the criteria of the Dutch and Belgian EAS laws are formulated. For example, the Dutch EAS law states that the unbearable suffering should be "without prospect of improvement", which should be determined based on the patient's medical diagnosis and prognosis (EuthanasiaCode, 2018, Dutch Act, 2002). Similarly, the Belgian EAS law states that the patient has to experience "constant and unbearable physical or psychological suffering that cannot be alleviated" (Belgian Act, 2002).

While the unbearable suffering requirement relies primarily on the patient's own assessment of the quality and severity of their suffering, whether or not that suffering can be alleviated depends on a physician's assessment of possible treatments and their effects (EuthanasiaCode, 2018, Raus *et al.*, 2021). However, to the extent that the irremediability requirement should do its own work and not be conflated with unbearable suffering, clear definitions of both requirements are needed. The two requirements are often regarded as interrelated in practice and in guidance about psychiatric EAS, in ways that might undermine their value as separate legal and ethical requirements. *Physician*-subjective components of assessments of unbearable suffering and irremediability, as well as specific guidance on these requirements, both contribute to the potential conflation of the two criteria in practice, as outlined below.

A first issue is the physician-subjective assessment of a patient's unbearable suffering. The empirical study outlined in Chapter 2 showed that judgments of the unbearable suffering requirement on the part of clinicians included possible countertransference issues, as opposed to purely subjective patient reports. The fact that the term "palpable" was used almost exclusively in persons with personality disorders, often by non-psychiatrists, shows that the pitfalls of

countertransference are not just a theoretical possibility. This is important because discussions about the lack of prospect of improvement of the patient's suffering is often presented in terms of a "patient-subjective" versus a "medically objective" dichotomy. However, the results of this study suggest that there is a *third* relevant axis, namely that of the physician-subjective assessment. This new dimension of physician subjectivity adds to the existing critique described by Dutch psychiatrists, that the interpretation of the "no prospect of improvement" component of the unbearable suffering criterion is becoming overstretched by emphasizing the [*patient*] subjective component (Onwuteaka-Philipsen *et al.,* 2017). While this could be framed in terms of as a shift toward greater patient determination (den Hartogh, 2017), physician-subjectivity seems problematic.

Therefore, guidelines on how to assess unbearable suffering, especially those intended for physicians more broadly like those issued by the RTE, can affect how clinicians evaluate psychiatric EAS requests, in ways that were not intended and probably not foreseen. This issue needs to be acknowledged and addressed. Furthermore, current guidance needs take into consideration that a majority of physicians performing psychiatric EAS evaluations are not psychiatrists. While guidelines issued by psychiatric professional organizations call for psychiatrists to recognize and address their own subjective reactions (Berghmans *et al.,* 2009, Vandenberghe *et al.,* 2017), non-psychiatrist physicians without this specific expertise might not be trained to do so.

A second issue is that physicians' subjective determination of unbearable suffering can influence how they assess irremediability, which guidelines consider to be primarily an objective, medical judgment. The study described in Chapter 2 found that in over a fourth of cases (26%), a physician considered a treatment option but then determined that it need not be tried, either because the physician thought the patient would not benefit from the treatment or because they appeared not motivated enough. For example, case 2016-01 offers a description of a situation in which the physician acknowledged the treatment options for the patient's personality disorder, but noting that it was "an open question whether the patient could cope with these treatments". A physician-subjective judgment about the patient's perceived ability to cope is conceptually problematic, because it does double duty in the EAS evaluation. On the one hand, the patient is said to suffer

unbearably because of their inability to cope. But on the other hand, this is regarded as a reason for judging that there are no available treatment options, which includes treatment options designed to improve coping. This is an example of how the irremediability requirement risks being reduced to, or conflated with, the assessment of unbearable suffering.

Current guidance on how to assess irremediability might actually contribute to this problem. For example, RTE guidance refers to a specific case to illustrate how irremediability should be defined in psychiatric EAS evaluations (EuthanasiaCode, 2018). But this is another example in which the physician (non-psychiatrist) uses their own perception of the patient's ability to cope to determine irremediability: "psychotherapeutic treatments would have little chance of success because of the patient's low coping capacity" (case 2016-78). In sum, existing guidance should direct sufficient attention to the interaction between clinical complexities and physicians' own interpretations and reactions, and the effects that these interactions can have on assessments of irremediability.

Recommendation No.2: Refining clinical interpretations of irremediability

"The precise contours of the requirement that no treatment options remain will have to be worked out in the future" was the conclusion of the section on irremediability and psychiatric EAS in *Asking to Die* (Thomasma *et al.*, 1998). Over two decades later, this is still very much the focus of discussion, as illustrated by the differences among existing guidelines about how irremediability should be interpreted and the extent to which the past treatments should be "evidence-based", "reasonable" or "acceptable to the patient" (FCECE, 2020, NVVP, 2018, Orde der Artsen, 2019, Vandenberghe *et al.*, 2017). This wide range of interpretations is grounded in different views on whether the assessment of irremediability should mainly rely on a clinical judgment or instead on patient preferences. This debate is only in its early stages, as described in Chapter 3, and is likely to continue in the future. A first step towards this conceptual discussion is to clarify what irremediability means in the *medical* sense when applied to psychiatric disorders. This can then serve as a basis for subsequent value judgments about whether or not available options are reasonable or acceptable to the patient and their physician.

This dissertation suggests several ways in which irremediability could to be refined in current guidance. First, guidelines can increase their evidence-based content and be clearer about what the field knows and does not know about the particular question of *predicting* chances of recovery of a certain psychiatric disorder. The evidence-based review described in Chapter 5 is an example, focusing on treatment-resistant depression. The same analysis and review can be done for other psychiatric conditions, such as bipolar, personality or psychotic disorders. This is important because comorbidity is the rule among patients requesting psychiatric EAS. For example, treatment studies targeting depression in combination with personality disorders are still lacking (Van and Kool, 2018), while this is an especially frequent combination among psychiatric EAS cases. Similarly, co-occurring psychiatric and somatic comorbidity interact in complex ways and are common in psychiatric EAS. Current gaps in scientific knowledge about treatment of psychiatric and somatic comorbidities needs to be acknowledged. Hence, guidance about how to determine chances of recovery should be more informative of current knowledge as well as of its limits and gaps.

Second, current guidelines focus on existing treatment options for the underlying psychiatric conditions when addressing evaluations of irremediability (Berghmans *et al.*, 2009, NVVP, 2018, Vandenberghe *et al.*, 2017). However, if indeed there is overlap between persons requesting psychiatric EAS and those engaging in suicidal behavior, it is important not to overlook the existing treatments for suicidal ideation and behavior, particularly in women, due to their known higher rates of suicidal ideation and behavior. This issue of potential unmet needs among persons requesting psychiatric EAS is particularly salient since in clinical practice a majority of patients do not receive adequate treatment of their suicidal ideation and behavior (O'Connor and Nock, 2014). Furthermore, the empirical study in this project suggests that evidence-based treatments for suicidal ideation and behavior are virtually never reported as being attempted even as suicidal behavior, including past suicide attempts, were frequent in past medical histories. Therefore, guidelines about psychiatric EAS should address the question of whether suicidal ideation and behavior is a clinical target of treatment for clinicians to consider during psychiatric EAS evaluations.

Finally, the finding described in Chapter 2 that specific and highly effective evidence-based treatments for personality disorders were virtually never tried, can also be indicative of knowledge gaps of evaluating physicians. This issue is important, especially since a majority of psychiatric EAS evaluations are performed by non-psychiatrists. While evaluating physicians are likely to consult a psychiatrist - or in the case of Belgium, are mandated to do so by law- it remains important that the physician performing the EAS evaluation is fully informed of the current state-of-the-art. Hence, the question is whether current guidelines are sufficiently tailored to physicians who perform psychiatric EAS evaluations in practice. For example, while an exhaustive overview of treatments for each mental disorder might not be possible nor desirable, guidance could benefit from clarifying what the state-of-the-art for the most common psychiatric conditions looks like.
However, among psychiatrists and non-psychiatrists alike, a pressing empirical question is whether clinicians have sufficient knowledge of existing guidelines, and if so, whether they think the amount of information provided is appropriate. A Dutch government survey study showed that only one *fourth* of psychiatrists was familiar with the Code of Practice guidelines issued by the RTE in 2015 (Onwuteaka-Philipsen *et al.*, 2017). No data are available of clinicians' knowledge of the guidelines focusing on psychiatric EAS evaluations, like those issued by the Dutch and Belgian (Flemish) Psychiatric Associations.

Recommendation No.3: Including greater expertise over longer time periods

The question of whether procedural safeguards as established by law are sufficient is ongoing, especially as they relate to involving specific expertise and sufficient time between the request and the time of death. The results of the study described in Chapter 2 support the proposals to involve greater psychiatric expertise and lengthier time periods for the psychiatric EAS evaluations (Gastmans, 2018, Vandenberghe *et al.*, 2017). Several empirical findings suggest that greater psychiatric expertise is needed. First, the high rates of psychiatric comorbidities as well as the high rates of psychiatric and somatic comorbidities point to the complexity of clinical histories of patients requesting psychiatric EAS, one that requires expertise. Second, complex interpersonal dynamics and their influences on the psychiatric EAS evaluations, as described earlier, can be difficult to discern and address appropriately without adequate and specialized training. Third, due to the physician-centeredness of the EAS laws, patients are more likely to be seen by physicians,

regardless of their degree of expertise, than by non-physician mental health professionals. However, many physicians have less affinity with the management of mental disorders than trained mental health professionals. Finally, the study found that current involvement of psychiatrists during psychiatric EAS evaluations is lower than what is advised for in existing guidance: the physician performing the EAS evaluation was a psychiatrist in only 30% of cases, there was no treating psychiatrist involved in over a third of cases (36%) and the advised combination of both an official EAS psychiatric consultant and a second opinion psychiatrist occurred in only 20%.

The second proposal calls for more lengthy evaluations, which is also supported by the findings of the empirical study showing that evaluation periods remain relatively short in the Netherlands (where, unlike in Belgium, no waiting time is required by law for psychiatric EAS cases). Exact timing between the very first request and the EAS itself was difficult to trace in the case reports, because the initial timing was not always specific. However, the time between the evaluation by the official EAS consultant and time of death could be determined. This time period was less than one month in 65% of cases. Belgian data suggest that in 60% the period between written request and time of death was less than three months, while the period of one year as advised by the Flemish Psychiatric Association guidance, occurred only in 15% (Raus *et al.*, 2021).

Finally, calls for greater expertise and for longer waiting times are also supported by the results from Chapter 6 about the similarities between the process of requesting psychiatric EAS and the suicidal process. How much similarity these *processes* share with psychiatric EAS requests is still largely unknown, but the results of the analysis suggest that there might be greater overlap than previously assumed, especially in women who have known protracted suicidal processes (Schrijvers *et al.*, 2012). Indeed, evidence about suicide suggest that suicidal behavior is rarely an impulsive action occurring without preparation or serious planning. To distinguish between the two requires specific expertise. Hence, although a waiting period, e.g. the one-month period as stipulated by the Belgian EAS law, might be a safeguard against impulsive decision-making broadly defined, it might not *in itself* be a sufficient safeguard to discern persons who would otherwise be considered suicidal.

Broadening the ethical debate about psychiatric EAS

Recommendation No.4: Including all stakeholders involved

The systematic review of reasons found that overall, the debate is in its early stages, with relatively little direct engagement between authors. A first point to address relates to the form of the ethical debate about psychiatric EAS, which relies heavily on reasons put forward by non-clinicians, mostly from Anglophone countries. Clinicians (mainly physicians) have participated in the debate primarily through short, commentary-type articles. To achieve a more balanced and in-depth discussion, more engagement is needed from authors from a wide range of countries and backgrounds. For example, more input from a broad range of clinicians (e.g. psychologists and social workers) through full-length articles can help attending to the subtleties and complexities of clinical practice and associated ethical questions.

But the systematic review also points to other gaps in terms of involvement: perspectives from patients and scholars with lived experience is virtually non-existent. However, as a general principle, including patient/service user perspectives is both warranted and desirable. "Nothing about us without us" is a widespread principle that originated in the disability community, which calls for *direct* participation of members of a group affected by a particular policy (Charlton, 1998). The reasons for doing so include respect for the agency of the members of that group, as well as epistemological reasons for drawing from different sources of knowledge. In fact, some sources of information might not be available to scholars without lived experience, clinicians and non-clinicians alike, but are nonetheless crucial for a sound debate. The debate also calls for *indirect* patient participation, e.g. through empirical research on their attitudes and experiences, which will be discussed below (see Recommendation No. 7).

Recommendation No. 5: Addressing shortcomings of the non-discrimination argument

Beside broadening the type of scholars involved, the ethical debate about the permissibility of psychiatric EAS also needs further expansion and refining of its theoretical ethical content. In the Netherlands, psychiatric EAS was de facto legalized after the Dutch Supreme Court ruling on the

Chabot case that a "non-somatic" (i.e. mental) origin of suffering can justify invoking the so-called defense of necessity. Jurisdictions considering extending access to EAS to non-terminal illness have an opportunity to make policy decisions based on a more in-depth and comprehensive debate on the matter. The systematic review maps the ethical debate about the permissibility of psychiatric EAS, but does not assess the quality of the reasons provided. While the most commonly presented reasons are more likely to have had greater prominence, they are not necessarily the soundest arguments. Hence, the debate needs further analysis of its existing arguments as well as addressing its current gaps. The main suggested venues for further analysis are outlined below.

The non-discrimination argument about whether or not EAS for physical, terminal disorders should be extended to non-terminal, psychiatric disorders is a forceful argument that figures prominently in the debate. The argument is valid in that the conclusion follows from its premises, assuming its premises are true. However, whether it is sound remains to be proven; in fact, its major shortcoming is that each premise is controversial in itself and/or needs further analysis. The argument is structured as follows: (P1) EAS for terminal, physical illness is permissible; (P2) Its ethical justification in these cases is suffering; (P3) There are no relevant differences between mental and physical suffering; (P4) The consequences that arise as a result of permitting the practice do not outweigh the merits. Hence, it concludes, not allowing psychiatric EAS amounts to discrimination of persons with psychiatric disorders. The main shortcoming and the most urgent to address relates to P3 and P4, which will be the focus here.

The main problem with the argument is that it is ambiguous: its central focus is on suffering (i.e. that there are no relevant differences between mental and physical suffering), but it could also mean that there are no relevant distinctions between mental and physical *disorders*. The latter interpretation is arguably more tangible and salient for policy purposes. However, it has received relatively little attention in the debate. The systematic review of reasons showed that while many, especially non-clinicians, argued that "mental suffering is as bad as physical suffering", there was virtually no objection to this claim. At the same time, while clinicians more often evoked reasons relating to differences between mental and physical disorders (and virtually never in terms of suffering), full-fledged argumentation was lacking. Another indication that this topic is of clinical and ethical relevance is the stark difference between Dutch physicians' support for EAS based on

a mental disorder (34%) compared to a physical disorder (82%), which was closer to their support for EAS in terminal disorders like cancer (85%) (Bolt *et al.*, 2015). This suggests that clinicians consider the distinction between mental and physical disorders to be important, and separate from the distinction between terminal and non-terminal physical disorders.

The question traces back to complex and contentious philosophical discussions about the nature, conceptualization and treatments of mental disorders. An in-depth discussion of this issue is beyond the purview of this dissertation. The point is that, while it is widely accepted that mental states derive from or "supervene on" brain states, the unsettled question is whether mental disorders differ from physical disorders in ways that are relevant for practical, policy making purposes, and if so, how. This is the topic of important ongoing discussions within the field of philosophy of psychiatry and philosophy of mind (Banner, 2013, Cooper, 2014, Crossley *et al.*, 2015, Kendell, 2001, Kendler *et al.*, 2011, White *et al.*, 2012). Hence, assuming that it is a settled matter, as is often the case in the debate about psychiatric EAS, is mistaken. Rather, these discussions should be incorporated into the debate about whether or not psychiatric EAS is permissible.

Finally, the difference between physical and mental disorders can also be addressed from the viewpoint of the consequences that the different applications would yield (i.e. often expressed in "risk of error"). Factoring in the consequences of permitting EAS based on a mental disorder is important and necessary when determining the moral permissibility of the practice. However, the last premise of the non-discrimination argument assumes that consequences arising as a result of permitting the practice do not outweigh its intended merits. This raises two questions for further analysis. First, this implies that we *know*, e.g. from empirical studies, the magnitude of the consequences of permitting psychiatric EAS in order to establish that it does not outweigh its merits. However, the effects of permitting the practice are still largely unknown. Second, even if we were to know exactly what the magnitude of the effects would look like, the argument assumes, it does not matter because the right to EAS trumps all possible consequences. But that can only be true if EAS actually is a basic human *right*. While in the Netherlands and Belgium as well as the United States, EAS is not considered a right, discussions of the contrary are ongoing in Canada and Germany (CCA, 2018, EuthanasiaCode, 2018, Horn, 2020, Jones *et al.*, 2017, Lemmens *et al.*,

2018). Hence, the argument needs further discussion on whether not grounding access to EAS based on mental disorders amounts to unjust discrimination.

Recommendation No.6: Incorporating ongoing discussions about personal recovery

Another important gap in the ethical debate is the lack of discussion or mention of recovery model(s). The "recovery model" originated almost three decades ago in response to the prevailing "medical model" of mental disorders, with the aim of emphasizing hope, self-empowerment, social support and functioning, rather than mere symptom reduction (Ahmed *et al.*, 2012, Anthony, 1993, Leamy *et al.*, 2011, Warner, 2009). Discussions about personal recovery are salient to the debate about psychiatric as they pertain to questions of autonomy, suffering and irremediability. For example, an important but underexplored issue in the debate about psychiatric EAS is how to reconcile the practice with questions of autonomy and self-determination. Within the debate, questions of autonomy are framed mainly in terms of decision-making capacity and rationality, i.e. the question of whether a person with a mental disorder can have a rational wish to die. This refers to autonomy in the so-called negative sense of non-interference. i.e. the freedom to make a choice free from interference of others. However, little attention has been paid to autonomy in the positive sense, namely questions of individual flourishing and living up to one's goals and values, which is what personal recovery is about. Furthermore, recovery models emphasize different conceptualizations of what it means to have a mental disorder and to recover from them, as will be outlined in the next section. Despite the relevance of these discussions for the debate about psychiatric EAS, recovery is only mentioned in guidelines for clinicians on how to promote "recovery-oriented care" ("*herstelondersteunende zorg*" in Dutch) during psychiatric EAS evaluations (NVVP, 2018, Vandenberghe *et al.*, 2017). However, how the conceptual foundations of the recovery model(s) ought to be incorporated in the ethical debate about the *permissibility* of psychiatric EAS, is another question, one that is rarely -if ever- mentioned in the debate.

To lay out how this gap can be bridged, it is important to take a step back by describing the two different interpretations of the recovery model. While both aim at countering the prevailing medical model of mental disorders, they differ in the ways in which they conceptualize mental disorders and their effects. According to the more widespread interpretation, recovery should not

be defined merely in terms of symptom reduction, but should include symptom management and improved functioning. For example, the shift to "difficult-to-treat" terminology as opposed to "treatment-resistant" is consistent with this interpretation of recovery (McAllister-Williams *et al.*, 2020, Rush *et al.*, 2019). Another example is the emerging field of "palliative psychiatry", with its focus on patient-centeredness and quality of life (Decorte *et al.*, 2020, Strand *et al.*, 2020, Trachsel *et al.*, 2016). The recovery model defined in this way views mental disorders as something to be treated, but treatment should not be limited to symptom reduction. It promotes interventions like addressing stigma, promoting a fulfilling life despite not being formally "cured", or involving social support within the patient's treatment trajectory.

The second interpretation of personal recovery questions the very idea that mental disorders (often referred to as mental differences instead) are necessarily gloomy, bad or harmful entities people "suffer" from. This interpretation is the one we find in the earlier descriptions of recovery (Anthony 1993). Proponents of the neurodiversity model and Mad Studies fall under this category. They claim that mental disorders, such as autism or psychotic disorders, can instead be a positive part of a person's identity and as such, not necessarily something one wants or needs to recover from. Similarly, Dutch psychiatrist van Os has argued that discussions about autism or schizophrenia have evolved from the idea that these are serious, incurable disorders to that of a spectrum consisting of traits many people share across the population (van Os, 2016). Insofar as these models challenge the very assumption that a mental disorder necessarily leads to unbearable mental suffering that cannot be alleviated, these discussions are salient for the debate about psychiatric EAS. For example, the paradigm case of "the patient with treatment-resistant depression" often invoked by philosophers in the debate, mostly assumes a somber and static view, one that does not necessarily reflect the wide range of experiences of persons with serious depression.

A discussion about the respective merits and challenges of these various models is beyond the purview of this project. However, scholars involved in the debate about psychiatric EAS cannot ignore these important ongoing discussions. The ethical debate about psychiatric EAS needs to be complemented by the different perspectives the recovery models have to offer. An example of why this question matters was given during the Tine Nys court trial in January 2020. Tine Nys was a

38-year old woman who received psychiatric EAS in 2010 and whose family took the case to court. One of the main points of contention during the trial was the interpretation of irremediability in this particular case. Some questioned whether she received sufficient treatment for her autism spectrum disorder, given the short period (i.e. two months) between her diagnosis and the time of death (Van Thillo and Beel, 2020). Others pointed to the fact that many within the autism community view autism as part of one's identity, not as a disorder, much less an irremediable one (Schaerlaken, 2020). This illustrates the tension between cure and recovery, one that the scholarly debate about psychiatric EAS needs to begin paying attention to. In sum, the point here is not to trivialize or romanticize mental disorders. Rather, it is about the urgent need to broaden and shape current discussions about psychiatric EAS in ways that acknowledges and brings together advances in related and relevant fields.

Recommendation No. 7: Integrating empirical evidence in ethical argumentation

Having addressed the main conceptual shortcomings of the ethical debate, I will briefly turn to its main empirical gaps. Overall, the ethical debate is largely conceptual, focusing on idealized cases, with only limited reference to empirical evidence or contextual factors. While this is a common challenge in the field of bioethics (Solomon, 2005), this issue is especially salient in the context of psychiatric EAS. Hence, the gap between the conceptual and the practical needs to be bridged. One way to achieve this is by testing the assumptions underlying certain arguments. For example, when empirical assumptions are made about psychiatric disorders, evidence about the current state of the art needs to be incorporated. Chapter 5 in this dissertation describes an example of testing the empirical assumptions about predictions of prognosis and chances of recovery in treatment-resistant depression. This type of analysis needs to be applied to other psychiatric conditions as well, such as personality disorders, schizophrenia or PTSD. Similarly, consequentialist claims about the effects of psychiatric EAS need to be tested. These include – but are not limited to – the effects of the practice on the patient-physician relationship, on mental health care more broadly and on population-level suicide rates.

A second way to bridge the empirical gap is to expand and incorporate qualitative research about the knowledge, lived experiences and attitudes of those participating in psychiatric EAS

evaluations. While several interview studies with physicians have been published, including psychiatrists and psychiatric nurses (Bolt *et al.*, 2015, De Hert *et al.*, 2015, Evenblij *et al.*, 2019, Onwuteaka-Philipsen *et al.*, 2017, Pronk *et al.*, 2019), similar studies involving patient perspectives are still lacking. In fact, only one Belgian empirical study consisted of a qualitative study of patients' written "testimonials" describing their reasons for requesting psychiatric EAS (Verhofstadt *et al.*, 2017). To date, there are no studies directly involving patients, e.g. through in-depth interviews or focus groups. Similarly, empirical studies involving patient families are currently lacking. The extent to which families should be involved in psychiatric EAS requests is an important topic of debate, as illustrated by high profile media cases, such as the Tine Nys and Godelieve De Troyer cases (Cheng, 2019, Truyts, 2020). Professional organizations increasingly and explicitly incorporate the issue in their guidelines (NVVP, 2018, Orde der Artsen, 2019, Vandenberghe *et al.*, 2017). Therefore, understanding patient and their families' perspectives and expectations is crucial for ongoing discussions about this issue.

Focusing on the tension between psychiatric EAS and suicide prevention

Recommendation No. 8: Examining psychiatric EAS through the lens of suicide

The tension between psychiatric EAS and suicide prevention is important from a public policy perspective. Discussions about psychiatric EAS and suicide have so far mainly focused on their differences in terms of the processes, patient clinical profiles and clinicians' attitudes (Creighton *et al.*, 2017, Pronk *et al.*, 2020, van Veen *et al.*, 2019). However, the analysis of the gender gap in psychiatric EAS outlined in Chapter 6 suggests that there might be more similarities in clinical profiles than previously assumed. The implications for psychiatric EAS are considerable, especially given that so far, the debates and guidelines alike have not focused on suicidal ideation and behavior. Perhaps this relative silence stems from contentious international discussions about whether or not EAS should be considered a form of suicide or rather as aid-in-dying (Friesen, 2020, Hedberg and New, 2017, Snyder Sulmasy and Mueller, 2017). In the context of terminal illness, this is mainly a theoretical philosophical discussion. However, in the context of psychiatric illness, this raises direct consequences for public health policy, which the debate about psychiatric EAS should not overlook. For example, it has consequences for how clinical management of

suicidal behavior is incorporated in psychiatric EAS evaluations and how waiting times and impulsive decision-making in psychiatric EAS evaluations is being addressed. More generally, it suggests that the pool of patients potentially requesting psychiatric EAS at some point is perhaps larger than expected, raising various policy issues, including how to ensure continued psychiatric expertise if the number of requests increase. At the same time, it calls into question current ways in which suicidal behavior in clinical practice is being addressed at both ends of the spectrum: in terms of unmet treatment needs of suicidal patients as well as in terms of practices used in treatment, including coercion. The concrete ways in which this tension can be addressed are described in the following section.

Recommendation No. 9: Clarifying conceptually inconsistent notions of informed consent

The tension between psychiatric EAS and suicide prevention also raises clear conceptual questions, if patients requesting psychiatric EAS are indeed similar to those engaging in suicidal behavior. In particular, it raises questions about the standards for an *informed choice* in both psychiatric EAS and suicide prevention. The systematic review shows that many accept the view that a request for psychiatric EAS is not pathological per se and not an indication of incapacity. However, the opposite assumption is held when treating suicidal persons: clinicians typically treat suicidal persons as if they were incapacitated and their desire to die pathological. Hence, in practice, a person with a psychiatric disorder who wants to die is treated differently, depending on how they express their wish to die. For example, while suicidal behavior might lead to an involuntary hospitalization, a request for psychiatric EAS would likely not. So far, the way to address this tension has been to distinguish between the two situations, by characterizing suicide as impulsive and euthanasia as carefully planned (Creighton *et al.*, 2017, den Hartogh, 2016). However, the analysis described in Chapter 6 suggests that this distinction is not empirically grounded. The presumed distinction is not tenable and does not adequately address the tension between psychiatric EAS and suicide prevention. Rather, if the clinical profiles of patients and the processes they undertake to bring about their death tend to be similar in both psychiatric EAS and suicide, this raises an important and underexplored question, namely what the standards should be for an informed choice in both psychiatric EAS and suicide prevention. Hence, these different conceptions of informed consent call for an urgent reexamination of how we should address each

situation. This is of salient importance given that the United Nations Convention on the Rights of Persons with Disabilities, ratified by over 160 countries worldwide, adopts a more radically person-centered conception of autonomy, prohibiting the use of coercion or involuntary treatment (Appelbaum, 2016, Freeman *et al.*, 2015). Yet, what this implies for countries that have ratified it remains an open question (Dom, 2015, Kelly, 2014), particularly for countries where the tension between psychiatric EAS and suicide prevention exists.

The tension calls for determining an appropriate set of necessary and sufficient conditions for an informed request for psychiatric EAS. The legal requirement in the Belgian and Dutch law that a psychiatric EAS request be "voluntary and well-considered" reflects the intent of these EAS laws to adhere to the doctrine of informed consent. This includes the following conditions: the person needs to be adequately informed and comprehend the decision at stake, she should have decision-making capacity and the decision should be voluntary (Beauchamp and Childress, 2019). While the EAS laws do not specify *how* the "voluntary and well-considered request" requirement should be assessed, Belgian and Dutch guidelines require that the so-called four abilities model be used for assessing decision-making capacity (EuthanasiaCode, 2018, Vandenberghe *et al.*, 2017). That is, for any given decision, a person has to show the ability to: (a) understand, (b) reason, (c) appreciate how the decision applies to them and (d) communicate their choice (Grisso and Appelbaum, 1998). However, there are challenges with how this requirement is being assessed in practice (Doernberg *et al.*, 2016, Schweitser *et al.*, 2020) and important questions about how it ought to be assessed, as described in Chapter 3.

First, there is a question of how the voluntary and well-considered requirement is being assessed *in practice*. Evidence about the practice of psychiatric EAS suggests that the way clinicians assess decision-making capacity varies widely. In a first patient-level analysis of 66 cases, over half (55%) of the assessments of patients' capacity consisted of global clinical judgments (Doernberg *et al.*, 2016). While almost a third (32%) included some statements about the specific abilities that are standardly used to assess capacity, only 8% mentioned all four abilities. A recent interview study with twenty-two Belgian psychiatrists and neurologists showed that most of the physicians described that formal capacity assessments were not part of their training (Schweitser *et al.*, 2020). Only a minority was familiar with common clinical tools and scales used to assess decision-making

capacity, like the MacArthur Competence Assessment Tool. Therefore, one pertinent question is whether commonly used tools proven to be empirically valid - that is, proven to capture the four abilities as they are supposed to- are properly applied in practice.

Second, a separate question is whether the four abilities model captures what really *matters* about decision-making capacity in the context of psychiatric EAS. In other words, the question of what the standards for a voluntary and well-considered request should be. Whether the four abilities model is sufficient for defining decision-making capacity is a topic of ongoing discussion (Hawkins and Charland, 2020). Factors such as emotions, authenticity, personal values and beliefs have been pointed to as potential important challenges to the four abilities model (Buchanan and Brock, 1989, Hawkins and Charland, 2020, Kim, 2016b). The underexplored question is how this applies to the context of psychiatric EAS. Interview studies as well as guidelines on the topic suggests that views vary on how decision-making capacity should be assessed in the context of psychiatric EAS (Schweitser *et al.*, 2020, Vandenberghe *et al.*, 2017). In fact, some clinicians adopt a more inclusive, but less defined view in which they rely on their own intuitions and experience (Schweitser *et al.*, 2020). This lack of consensus in clinical practice is reflected in the ethical debate about the practice of psychiatric EAS, which shows that there is considerable disagreement about whether the same standards should apply for EAS as for other decisions in healthcare and if so, whether the threshold for each ability should be the same or different.

Hence, we need to reconsider the standards for an informed request for psychiatric EAS. In practice, there is no consensus about how exactly, ethically speaking, the requirement for an informed psychiatric EAS request should be defined. A first question is what *standards* should apply to decision-making capacity in this context. So far, the four abilities model constitute the prevailing assessment tool according to the guidance on psychiatric EAS. However, current standards for suicide prevention suggest that this may not be sufficient. Several candidate factors have been proposed as challenges to the four abilities model (e.g. the role of emotions, values and authenticity), raising the question of whether and how this applies to psychiatric EAS. Second, a main issue warranting analysis is that of the *threshold* for decision-making capacity in the context of psychiatric EAS. An assessment about decision-making capacity is a yes-or-no ruling: relative to a particular decision, a person either does or does not have capacity. This has raised the question

of whether there should be a single or a different threshold, depending on the decision at stake. The systematic review of reasons has shown how some authors argue that the threshold for psychiatric EAS should be higher than in other healthcare decisions, because the stakes are higher (i.e. death in the case of EAS). Others have called for a same threshold across the board, i.e. for a certain level of understanding, appreciation and reasoning that the person must have for any decision, including psychiatric EAS. The threshold question should be examined in relation to its application in suicide prevention.

Third, the threshold question is intrinsically linked to another theoretical question, namely that of the *value* of the outcome at stake, i.e. in this case, the value of death. In the context of suicide prevention, death is considered a harm from which the person should be protected. But in the context of psychiatric EAS, it is typically not considered as such. The main question here is whether the value associated with death can be determined in the same way in both situations. Finally, the doctrine of informed consent requires decision-making capacity as a prerequisite, but an important additional necessary condition is that this decision be voluntary. The systematic review showed that voluntariness is virtually never mentioned in the ethical debate about psychiatric EAS. Both external and internal factors can undermine voluntariness, but most discussions focus on external voluntariness, such as coercion or undue inducement. Similarly, psychiatric EAS guidelines state that the request should be free of pressure and interference from third parties (EuthanasiaCode, 2018, Vandenberghe *et al.*, 2017). But little has been said about what it means for a decision to be free of *internal* pressure that could undermine one's voluntary decision. While it is often assumed that suicidal ideation or behavior stems from internal influences, what these factors are and whether they apply to psychiatric EAS needs further analysis. Solving this complicated question may not be possible, but identifying what factors might play a role is warranted. Hence, further analysis and proposal for the necessary and sufficient conditions for a voluntary and well-considered request for psychiatric EAS is needed.

In sum, the tension between psychiatric EAS and suicide prevention constitutes a unique ethical dilemma with direct practical implications, warranting further clinical-ethical analysis. Insights into how this tension might be addressed will have direct implications, both for the practice of psychiatric EAS as for the treatment of persons with suicidal ideation and behavior.

Recommendation No. 10: Investigating how suicide risk factors apply to psychiatric EAS

The similarities between persons requesting psychiatric EAS and those engaging in suicidal behavior also raise specific empirical questions that need urgent study. For example, we need to systematically analyze known population-level suicide *risk factors* and how they apply to persons requesting psychiatric EAS. One example of such risk factor is media reporting and its effect on imitation behavior or social contagion, especially in subpopulations with greater risk of imitation behavior, such as young adults (Turecki *et al.*, 2019). Furthermore, given the high prevalence of women among psychiatric EAS cases, it is important to focus on gendered social determinants, including but not limited to gender-based violence, and how they may affect requests for psychiatric EAS. Finally, we need research on prevailing gendered social-cultural attitudes and norms towards suicidal behavior and how they may translate to psychiatric EAS.

Methodological Considerations and Potential Limitations

The overall objective of this project was to gain an in-depth understanding of the practice of psychiatric EAS as well as of the scholarly ethical debate about this issue. The project aimed at identifying the currently underexplored but relevant clinical-ethical issues with important policy implications. To reach this objective, the project comprised of an empirical and a theoretical-ethical research line, which together laid the foundation for ethical analysis of three subdomains of policy and practical relevance.

This PhD project and the methods it used have some overall limitations. First, because the focus of this project was on psychiatric EAS, as opposed to EAS more broadly, the project focused on the requirements as they apply to psychiatry EAS. Hence, this project did not focus on the more general regulatory aspects of the practice of EAS, nor does it provide a comprehensive evaluation of the EAS laws in the Netherlands or Belgium, their application and the legal question of whether they should be amended or repealed. Rather, the findings and recommendations describe concrete ways in which the international scholarly debate and existing guidance about the practice of psychiatric EAS can be informed and improved, in an evidence-based and ethically sound manner.

Second, throughout Chapters 2-6, this project has mainly analyzed the clinical and ethical aspects of the substantive requirements of irremediability and unbearable suffering. This means that the third key requirement, that the request be voluntary and well-considered, has not been the focus of clinical-ethical analysis. However, that is an important topic in itself, which warrants further study. The systematic review of the ethical debate shows that it remains an important and contentious issue among scholars. The fact that it did not emerge as a major theme in the empirical study could be an artefact of how decision-making capacity is being assessed in psychiatric EAS evaluations and clinicians' general knowledge and skills regarding the topic (Doernberg *et al.*, 2016, Schweitser *et al.*, 2020). Hence, as outlined in the Recommendations section, this topic warrants further analysis, especially as it relates to the tension between psychiatric EAS and suicide prevention.

Third, it is important to keep in mind that the available data on the practice itself remain limited overall and sample sizes are small. This means that hypotheses and conclusions based on the

empirical study should be interpreted with caution and are not generalizable to all psychiatric EAS cases. Furthermore, it does not provide information about cases that have been refused, or in which the person decided not to proceed with their EAS process. However, this type of research involving patient-level reports is of great social value, in that these reports are the best and only available source of data to study the Dutch practice. Given the high stakes, furthering our understanding of the practice is of paramount importance, even if this involves exploratory studies at the moment.

Fourth, the qualitative component of the empirical work in this project involved judgment and potential bias. To mitigate this risk, in the two studies involving qualitative content analysis (Chapters 2 and 3), data extraction was done by two independent reviewers and discrepancies were discussed involving a third reader. In the empirical study involving case reports, the two readers performing the coding, myself included, as well as the third reader, were trained psychiatrists and bioethicists. This allowed for developing a coding scheme and extracting data in a way that was both ethically relevant as well as sensitive to the clinical psychiatric complexities at stake. The primary aim of this type of qualitative analysis is to elucidate some of the ongoing processes in an open-ended, iterative and emerging manner. Hence, it serves the function of setting out further research lines, both conceptual and empirical, rather than that of generating generalizable facts.

Avenues for Future Research

This project provided novel insights into the practice of psychiatric EAS in the Netherlands, as well as the broader ethical debate about the issue involving different countries and scholars with different backgrounds. It provides concrete avenues for conceptual research in the near future, as outlined in the Recommendations section, including establishing adequate conceptual boundaries between unbearable suffering and irremediability in the context of psychiatric EAS, addressing the shortcomings of the non-discrimination argument, analyzing the potential strengths and weaknesses of the recovery models for the debate about psychiatric EAS, addressing the tension between psychiatric EAS and suicide prevention, and clarifying the related question of the necessary and sufficient conditions for an informed request for psychiatric EAS. It also provides venues for concrete empirical research, including describing patient perspectives and attitudes towards psychiatric EAS as well as their families' perspectives, testing the effects of psychiatric

EAS on patient-physician relationships, on mental health care and on population-level suicide rates, exploring clinicians' knowledge and attitudes towards existing guidelines, and investigating how suicide risk factors apply to psychiatric EAS.

However, this is by no means an exhaustive list. For example, other conceptual issues have received little attention so far in the debate, but warrant further analysis, including the question of whether there is a moral distinction between psychiatric EAS and refusal of life-sustaining treatment in persons with psychiatric disorders (and if so, what grounds that distinction). There are also a number of urgent avenues for empirical research, which have been called for previously, but which nonetheless this project also provides support for. This includes the need for anonymized Belgian case reports to be made available for research, as to ensure transparency and accountability of the practice in Belgium. In the Netherlands, current knowledge is limited to the cases that are made available by the RTE. More could be done to make *all* cases available for research, as to provide a more generalizable view of the practice. Furthermore, data should not be limited to cases in which the person died by euthanasia, but should also include cases in which the request was denied, or in which the request was granted but the person decided not to proceed. This type of information is crucial to fully understand the process of EAS evaluations in a way that does not only focus on persons who received EAS. So far, the type of data made available have allowed to unravel only a small proportion of the clinical and ethical complexities of the practice.

Finally, the practice of psychiatric EAS in the past decade, with its clinical, ethical, policy and legal challenges, has coincided with the international recognition that the field of psychiatry is at a turning point, which prominent scholars have regarded as a transition phase from which we can and ought to fundamentally rethink mental health practice (Gardner and Kleinman, 2019, Vanheule *et al.*, 2019). The developments of the past decade force us to acknowledge the limits of biological psychiatry and the fading of traditional psychiatry as it has been practiced over the past 50 years, and to move towards a more inclusive mental health care practice. Continued efforts should be deployed to meet the need of persons in mental health care, inpatient and in the community, to address all facets of mental suffering.

Conclusion

The practice of psychiatric EAS remains highly debated and controversial. The challenges associated with the practice have started to emerge over the last few years. This dissertation work has contributed to unravel some of its salient clinical, ethical and policy questions. First, based on patient-level case reports and subsequent ethical analysis, this work has characterized some of the clinical and ethical challenges associated with assessing irremediability and unbearable suffering and ways in which current guidance regarding these criteria can be amended. Second, it has mapped the international ethical debate about psychiatric EAS and outlined several suggestions for addressing the current shortcomings in both its form and content. Third, it has underscored the particular importance of the tension between psychiatric EAS and suicide prevention strategies, by demonstrating that there are more similarities in the two processes than previously assumed. This raises several implications for psychiatric EAS and public policy, and points to potentially inconsistent notions of informed consent in psychiatry, warranting further analysis.

List of Figures, Tables & Boxes

List of Appendices

Contributions

List of contributors

Marie E. Nicolini, MD, MSc
PhD candidate, Centre for Biomedical Ethics and Law
Department of Public Health and Primary Care
Faculty of Medicine, KU Leuven
Kapucijnenvoer 35 – Block 3 Box 7001
3000 Leuven, Belgium

Postdoctoral Fellow, Department of Bioethics
Clinical Center, National Institutes of Health
10 Center Drive, Bldg 10, Room 1C118
Bethesda, MD 20892, USA

Chris Gastmans, PhD
Promotor, Centre for Biomedical Ethics and Law, Head
Department of Public Health and Primary Care
Faculty of Medicine, KU Leuven
Kapucijnenvoer 35 – Block 3 Box 7001
3000 Leuven, Belgium

Scott Y.H. Kim, MD, PhD
Co-promotor, Department of Bioethics, Faculty
Clinical Center, National Institutes of Health
10 Center Drive, Bldg 10, Room 1C118
Bethesda, MD 20892, USA

John Peteet, MD
Department of Psychiatry, Associate Professor
Harvard Medical School and Brigham and Women's Hospital
75 Francis Street

Boston, MA 02115, USA

Kevin Donovan, MD, MA
Center for Clinical Bioethics, Head (until Oct 2020)
Georgetown University
Bldg. D., Suite 236, 4000 Reservoir Road
Washington, D.C. 20007, USA

Madison Churchill, MA
Research Associate, Department of Bioethics
Clinical Center, National Institutes of Health
10 Center Drive, Bldg 10, Room 1C118
Bethesda, MD 20892, USA

Emma Jardas, MA
Postbaccalaureate Fellow, Department of Bioethics
Clinical Center, National Institutes of Health
10 Center Drive, Bldg 10, Room 1C118
Bethesda, MD 20892, USA

Carlos A. Zarate, MD
Section on the Neurobiology and Treatment of Mood Disorders, Chief
Experimental Therapeutics and Pathophysiology Branch, Chief
National Institutes of Mental Health
6001 Executive Boulevard, Room 6200, MSC 9663
Bethesda, MD 20892, USA

Description of contributions

Marie Nicolini was the PhD-candidate who carried out the study "Euthanasia and Assisted Suicide for Psychiatric Disorders, Clinical and Ethical Perspectives" as the main researcher. This included designing, performing and reporting each study described in this dissertation, and the development of the manuscript. Marie Nicolini has published, submitted or will be submitting all reported studies to international, peer-reviewed journals as the lead author. During this PhD trajectory, Marie Nicolini received support and professional guidance from Chris Gastmans and Scott Y. H. Kim, respectively promotor and co-promotor. They each contributed to the development of each study as well as to the dissertation project.

Because qualitative content analysis carried out by two independent reviewers significantly strengthens the study's methodology, Marie Nicolini carried out data extraction with an additional reviewer in two studies: John Peteet (study described in Chapter 2) and Madison Churchill (study described in Chapter 3). Emma Jardas reviewed a specific section in the study described in Chapter 5 and described the findings of that section, including Table 5.2 and Appendix 5A. Finally, critical feedback for important intellectual content was provided by Kevin Donovan (study described in Chapter 2) and Carlos Zarate (study described in Chapter 5).

Conflicts of interest

No conflict of interest to report.

Curriculum Vitae

Marie Elisabeth Nicolini MD MSc

marie.nicolini@kuleuven.be; marie.nicolini@nih.gov

+1 301 219 4122

CURRENT POSITION

09/2020 – Present
Doctoral Researcher, Centre for Biomedical Ethics and Law
KU Leuven Department of Public Health and Primary Care, Leuven, Belgium

09/2020 – Present
Visiting Scholar, Department of Bioethics
National Institutes of Health Graduate Partnership Program, Bethesda, Maryland, USA

EDUCATION & TRAINING

05/2018 – 05/2021
PhD Candidate, Centre for Biomedical Ethics and Law
KU Leuven Department of Public Health and Primary Care, Leuven, Belgium
Advisors: Chris Gastmans, PhD (KU Leuven), Scott Y.H. Kim, MD, PhD (NIH)
Expected graduation date May 2021

09/2018 – 09/2020
Postdoctoral Fellow, National Institutes of Health Department of Bioethics
Clinical Centre, Bethesda, Maryland, USA
As an NIH Bioethics Postdoctoral Fellow, I conducted academic research in bioethics and participated in the Ethics Consultation service activities, Ethics Committee meetings, Institutional Review Board deliberations, seminars & journal clubs about bioethical issues related to clinical research & practice, genetics & emerging technologies, public health and health policy. www.bioethics.nih.gov

08/2012 – 07/2017
Residency, Psychiatry
KU Leuven, Faculty of Medicine, Leuven, Belgium

01/2012 – 06/2014
Erasmus Mundus Master in Bioethics
KU Leuven (Belgium), RU Nijmegen (the Netherlands) & University of Padova (Italy)

09/2008 – 06/2012
Doctor of Medicine
KU Leuven, Faculty of Medicine, Leuven, Belgium

09/2005 – 06/2008
Bachelor of Medicine
KU Leuven, Faculty of Medicine, Leuven, Belgium

PREVIOUS POSITIONS

09/2017 – 09/2018 **Kennedy Institute of Ethics, Visiting Scholar**
Georgetown University, Washington DC, USA

09/2017 – 03/2018 **Pellegrino Centre for Clinical Bioethics, Visiting Scholar**
Georgetown University, Washington, DC, USA

08/2016 – 07/2017 **Community Centre for Mental Health Care**
Psychiatry Residency, CGG-Leuven, Belgium

08/2015 – 07/2016 **Genetic Frontotemporal Dementia Initiative, Research investigator**
KU Leuven, Belgium
Multinational consortium in collaboration with University College London (London, UK)
fMRI study on emotional memory in C9orf72 mutation carriers in presymptomatic frontotemporal dementia and/or amyotrophic lateral sclerosis.
http://genfi.org.uk/index.html

08/2014 – 01/2015 **Department of Old Age Psychiatry & Psychiatric Liaison Unit**
Psychiatry Residency, University Hospitals Leuven

08/2013 – 07/2014 **Psychosis Care: Inpatient and Outpatient Early Intervention Program**
Psychiatry Residency, University Hospitals Leuven

01/2013 – 07/2013 **Emergency Psychiatric Services**
Psychiatry Residency, University Hospitals Leuven

08/2012 – 01/2013 **Acute Psychiatric Care Unit & Clinic for Mood and Anxiety Disorders**
Psychiatry Residency, University Hospitals Leuven

09/2011 – 06/2012 **Department of Paediatrics & Child Neuropsychiatry**
Internships at Agostino Gemelli University Polyclinic Rome (Italy) & University Hospitals Leuven

RESEARCH GRANTS

Spring 2021 **Institute for Medical Ethics and History of Medicine, Visiting Scholar**
Ruhr University Bochum, Germany; one- month funded research stay

09/2018 – 09/2020 **Department of Bioethics, Postdoctoral Fellowship**
National Institutes of Health, 2-year funded position (see above)

CERTIFICATES & LICENSES

01/2020 Ethical and Regulatory Aspects of Clinical Research Certificate
National Institutes of Health, Department of Bioethics; Seven 3h-sessions

08/2018 United States Medical License Examination
ECFMG Certificate Step 1, Maryland, USA

12/2017 Psychiatry Board Certification
National Board of Examiners, Belgium

09/2014–06/2017 Psychodynamic Psychotherapy, Postgraduate diploma course
Completed 2 of 4-year program, KU Leuven (Belgium)

PUBLICATIONS

Peer-reviewed journal articles

Kim S.Y.H., Mangino D., **Nicolini M.E**. (2020) Is this person with dementia (currently) competent to request euthanasia? A complicated and under-explored question. *Journal of Medical Ethics (Epub 2020 Aug 13)* http://dx.doi.org/10.1136/medethics-2020-106091

Grady C., Shah S., Miller F., Danis M., **Nicolini M.E.**, Ochoa J., Taylor H., Wendler D., Rid A. (2020) So much at stake: ethical trade-offs in accelerating SARS-Cov-2 vaccine development. *Vaccine* 38(41): 6381-6387 https://doi.org/10.1016/j.vaccine.2020.08.017

Nicolini M. E., Kim S.Y.H., Churchill M. E., Gastmans C. (2020) Should euthanasia and assisted suicide for psychiatric disorders be permitted? A systematic review of reasons *Psychological Medicine* 50(8): 1241-1256 https://doi.org/10.1017/S0033291720001543

Mangino D.R., **Nicolini M. E**, De Vries R.G., Kim S.Y.H. (2020) Euthanasia and assisted suicide of persons with dementia in the Netherlands *American Journal of Geriatric Psychiatry* 28(4): 466-477 https://doi.org/10.1016/j.jagp.2019.08.015

Nicolini M.E., Peteet, J.R., Donovan, G.K., Kim, S.Y.H. (2020) Euthanasia and assisted suicide of persons with psychiatric disorders: the challenge of personality disorders. *Psychological Medicine* 50(4): 575-582 https://doi.org/10.1017/S0033291719000333

Nicolini M. E., Gastmans C., Kim S.Y.H. (2019) Parity Arguments for 'Physician Aid-in-Dying' (PAD) for Psychiatric Disorders: Their Structure and Limits. *American Journal of Bioethics* 19(10): 3-7 https://doi.org/10.1080/15265161.2019.1659606

Nicolini M.E., Vandenberghe J., Gastmans C. (2018) Substance use disorder and compulsory commitment to care: A care-ethical decision-making framework. *Scandinavian Journal of Caring Sciences*. 32(3):1237-1246. 10.1111/scs.12548

Commentaries, correspondence & book reviews

Rid A., Shah S., Miller F., Danis M., **Nicolini M.**, Ochoa J., Taylor H., Wendler D., Grady C. (2020) Ethical trade-offs in vaccine development and distribution: Response to Gurwitz. *Vaccine* 39(2): 1028-1029 10.1016/j.vaccine.2021.01.020

Nicolini M.E., Wendler D. (2020) Inherent conflict of interest in clinical research: A call for effective guidance. *The American Journal of Bioethics* 20(10):94-96. https://doi.org/10.1080/15265161.2020.1806376

Kim Scott Y.H., **Nicolini M.E.,** Mangino D. R., De Vries R.G. (2020) What we can learn from published reports of euthanasia in persons with dementia: A reply to Marijnisssen et al. *American Journal of Geriatric Psychiatry* (Epub 2020 July 11) https://doi.org/10.1016/j.jagp.2020.07.005

Nicolini, M.E., Kim S. Y.H. Euthanasie bij persoonlijkheidsstoornissen (2019) *Neuron* https://www.neuron.be/nl/nieuws/medisch-nieuws/euthanasie-bij-persoonlijkheidsstoornissen.html [Dutch summary of the paper Euthanasia and assisted suicide of persons with psychiatric disorders: the challenge of personality disorders]

Nicolini, M.E. Ethische handvaten voor procedure gedwongen opname bij verslaving. Kiezen voor dialoog. *Zorgwijzer* (Zorgnet Icuro) [Dutch summary of the paper Substance use disorder and compulsory commitment to care: A care-ethical decision-making framework] https://www.zorgneticuro.be/sites/default/files/2018%20Zorgwijzer%2073.pdf

Nicolini, M.E. [Book review, Dutch] Wie wij zijn. F. Koerselman (2016). Prometeus Amsterdam. ISBN 978-90-351-3699-1, 255pp. *Tijdschrift voor psychoanalyse & haar toepassingen* (2018) 24(3): 216-218.

https://www.tijdschriftvoorpsychoanalyse.nl/inhoud/tijdschrift_artikel/PA-24-3-11/Wie-wij-zijn

WORK IN PROGRESS

Nicolini M. E., Gastmans C., Kim S.Y.H. Psychiatric euthanasia, suicide and the role of gender (*British Journal of Psychiatry, Forthcoming*)

Nicolini M.E., Jardas E., Zarate C.A., Gastmans C., Kim S.Y.H. Treatment-Resistant Depression and the Concept of Irremediability *(in preparation)*

Nicolini M.E. End-of-life care and Physician-Assisted Suicide in Persons with Dementia: Intersections of Law and Psychiatry *(Frontiers of Psychiatry, Revise and resubmit)*

CONFERENCE PRESENTATIONS

American Psychiatric Association Annual Meeting: Panel Presentation "Assisted Dying and Challenges with Mental Illnesses: Ethics, Evidence and Impact" (Gaind S., Brendel R., **Nicolini, M.**, Peteet J.). Virtual meeting - May 1-3, 2021.

World Congress of Bioethics. Paper presentation: **Nicolini M**., Kim S.Y.H., Churchill M.E., Gastmans C. Should Psychiatric Euthanasia Be Permitted? A Systematic Review of Reasons" Philadelphia, USA – virtual meeting; June 19-21, 2020.

Feminist approaches to Bioethics, World Congress. Paper presentation: **Nicolini M.E**., Gastmans C., Kim S.Y.H. Paper presentation: "Why Do More Women Die by Psychiatric Euthanasia?" Philadelphia, USA – virtual meeting; June 18, 2020.

American Psychiatric Association, Annual Meeting: Panel Presentation "Evolving Assisted Dying Policies and Challenges with Mental Illnesses: What If There Is No Goldilocks Solution?" (Panellists: Brendel R., Gaind S., **Nicolini M**.). Philadelphia, USA – virtual meeting; April 24-29, 2020.

Jewish Social Service Agency: **Nicolini M.** "Euthanasia and physician-assisted suicide: Overview of practices around the world and current challenges". https://www.jssa.org/events/?tribe_paged=1&tribe_event_display=list&tribe-bar-

date=2020-01-16 Rockville, Maryland, USA; Jan 17, 2020.

Inova Fair Oaks Hospital, Conversations in Ethics**: Nicolini, M.** "Physician-assisted suicide: an international perspective". Fairfax, Virginia, USA; Aug 29, 2019.

American Psychiatric Association, Annual Meeting: Panel Presentation "Physician Aid in Dying: A Closer Look at the Psychiatrist's Role" (Panellists: Brendel R., Gaind S., **Nicolini M.E**., Peteet J.) San Francisco; May 18-22, 2019.

American Society for Bioethics and Humanities, Annual Meeting: Paper Presentation **Nicolini M**.: "Euthanasia and assisted suicide for personality disorders". Anaheim, CA, USA; Oct 18-21, 2018.

Organization for Human Brain Mapping (poster presentation): "Neural and behavioural effects of emotion and object category on non-verbal memory" **Nicolini M**., Jastorff J., Sleurs C, Sunaert S., Vandenbulcke M., Van den Stock J. (KU Leuven, Belgium). Geneva, Switzerland; June 26-30, 2016

TEACHING EXPERIENCE

Penn Memory Centre Didactics: "Aid in dying in persons with dementia and related emerging ethical questions" UPenn, Pennsylvania, USA - virtual seminar; Aug 24, 2020.

NIH Summer Internship Program in Biomedical Research: Introduction to bioethics Bethesda Maryland, USA; August 2019.

American University Bioethics Seminar: Euthanasia and assisted suicide for psychiatric disorders, Washington DC, USA; March 5, 2019.

Pellegrino Centre for Clinical Bioethics: Teaching clinical ethics to medical students, Georgetown University, Washington DC, USA; Period Oct 2017-Jan 2018.

REVIEWER FOR

Psychological Medicine, American Journal of Bioethics Empirical, Trials
Narrative Inquiry in Bioethics

SKILLS & INTERESTS

Reading group	Co-founder DC Reading Group in Philosophy of Psychiatry (monthly meeting since Jan 2020)
Language Skills	English (Fluent); French, Dutch, Italian (Mother tongue level) Spanish, Modern Greek, Hindi (Basic-Intermediate)
Music Skills	Conservatory degree in Harpsichord (Leuven, Belgium)
Interests	Reading, learning languages, travelling, hiking

General reference list

Adams, M. & Nys, H. (2003). Comparative Reflections on the Belgian Euthanasia Act 2002. *Medical Law Review* **11**, 353-376.
Ahmed, A. O., Buckley, P. F. & Mabe, P. A. (2012). RECOVERY: International efforts at implementing and advancing the recovery model. *International Psychiatry* **9**, 4-6.
Allsopp, K., Read, J., Corcoran, R. & Kinderman, P. (2019). Heterogeneity in psychiatric diagnostic classification. *Psychiatry Research* **279**, 15-22.
Alonso, S. G., de la Torre-Díez, I., Hamrioui, S., López-Coronado, M., Barreno, D. C., Nozaleda, L. M. & Franco, M. (2018). Data Mining Algorithms and Techniques in Mental Health: A Systematic Review. *Journal of Medical Systems* **42**, 161.
Anestis, M. D., Soberay, K. A., Gutierrez, P. M., Hernández, T. D. & Joiner, T. E. (2014). Reconsidering the Link Between Impulsivity and Suicidal Behavior. *Personality and Social Psychology Review* **18**, 366-386.
Anthony, W. A. (1993). Recovery from mental illness: The guiding vision of the mental health service system in the 1990s. *Psychosocial Rehabilitation Journal* **16**, 11-23.
Appelbaum, P. S. (2016). Protecting the Rights of Persons With Disabilities: An International Convention and Its Problems. *Psychiatric Services* **67**, 366-8.
Appelbaum, P. S. (2017). Should Mental Disorders Be a Basis for Physician-Assisted Death? *Psychiatric Services* **68**, 315-317.
Appelbaum, P. S. (2018). Physician-assisted death in psychiatry. *World Psychiatry* **17**, 145-146.
Aviv, R. (2015). The Death Treatment. When should people with a non-terminal illness be helped to die? In *New York Times*.
Ayre, K., Owen, G. S. & Moran, P. (2017). Mental capacity and borderline personality disorder. *British Journal Psychiatry Bulletin* **41**, 33-36.
Bailey, N. W., Hoy, K. E., Rogasch, N. C., Thomson, R. H., McQueen, S., Elliot, D., Sullivan, C. M., Fulcher, B. D., Daskalakis, Z. J. & Fitzgerald, P. B. (2018). Responders to rTMS for depression show increased fronto-midline theta and theta connectivity compared to non-responders. *Brain Stimulation* **11**, 190-203.
Bailey, N. W., Hoy, K. E., Rogasch, N. C., Thomson, R. H., McQueen, S., Elliot, D., Sullivan, C. M., Fulcher, B. D., Daskalakis, Z. J. & Fitzgerald, P. B. (2019). Differentiating responders and non-responders to rTMS treatment for depression after one week using resting EEG connectivity measures. *Journal of Affective Disorders* **242**, 68-79.
Bamelis, L. L., Evers, S. M., Spinhoven, P. & Arntz, A. (2014). Results of a multicenter randomized controlled trial of the clinical effectiveness of schema therapy for personality disorders. *American Journal of Psychiatry* **171**, 305-22.
Banner, N. F. (2013). Mental disorders are not brain disorders. *Journal of Evaluation in Clinical Practice* **19**, 509–513.
Bares, M., Novak, T., Brunovsky, M., Kopecek, M. & Höschl, C. (2017). The Comparison of Effectiveness of Various Potential Predictors of Response to Treatment With SSRIs in Patients With Depressive Disorder. *Journal Nervous Mental Disease* **205**, 618-626.
Bares, M., Novak, T., Kopecek, M., Brunovsky, M., Stopkova, P. & Höschl, C. (2015). The effectiveness of prefrontal theta cordance and early reduction of depressive symptoms in the

prediction of antidepressant treatment outcome in patients with resistant depression: analysis of naturalistic data. *European Archives of Psychiatry Clinical Neuroscience* **265**, 73-82.
Bartlett, V. L. & Finder, S. G. (2019). "When the fall is all there is…": Refocusing on the critical (unique?) characteristic of "dying" in physician-aid-in-dying. *American Journal of Bioethics* **19**, 43-46.
Bateman, A. & Fonagy, P. (2009). Randomized controlled trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. *The American Journal of Psychiatry* **166**, 1355-1364.
Bateman, A. & Fonagy, P. (2015). Borderline Personality Disorder and Mood Disorders: Mentalizing as a Framework for Integrated Treatment. *Journal of clinical psychology* **71**, 792-804.
Bateman, A. W., Gunderson, J. & Mulder, R. (2015). Treatment of personality disorder. *Lancet* **385**, 735-743.
Bazan, A. (2015). Schrap euthanasie op basis van louter psychisch lijden uit de wet (Dec 8, 2015). In *DeMorgen*.
Beauchamp, T. L. & Childress, J. F. (2019). *Principles of Biomedical Ethics.* Oxford University Press: New York, USA.
Belgian Act (2002). 28 MEI 2002. Wet betreffende de euthanasie (Loi relative à l'euthanasie). Available at: http://bit.ly/2jVFeS0. For an unofficial translation of the Act in English, see Jones et al. 2017 (Appendix III, pp.305-315).
Berghmans, R., Huisman, J., Legemaate, J., Nolen, W. A., Polak, F., Scherders, M. J. W. T. & Tholen, A. J. (2009). Richtlijn verzoek om hulp bij zelfdoding door patiënten met een psychiatrische stoornis. Nederlandse Vereniging voor Psychiatrie (Dutch Psychiatric Association).
Berghmans, R., Widdershoven, G. & Widdershoven-Heerding, I. (2013). Physician-assisted suicide in psychiatry and loss of hope. *International Journal of Law & Psychiatry* **36**, 436-443.
Bernal, M., Haro, J. M., Bernert, S., Brugha, T., de Graaf, R., Bruffaerts, R., Lepine, J. P., de Girolamo, G., Vilagut, G., Gasquet, I., Torres, J. V., Kovess, V., Heider, D., Neeleman, J., Kessler, R. & Alonso, J. (2007). Risk factors for suicidality in Europe: results from the ESEMED study. *Journal Affective Disordorders* **101**, 27-34.
Black, I. (2012). Suicide assistance for mentally disordered individuals in Switzerland and the state's positive obligation to facilitate dignified suicide: Haas C. Suisse, Cour europeenne des droits de l'homme, 1re section (20 janvier 2011). *Medical Law Review* **20**, 157-66.
Blikshavn, T., Husum, T. L. & Magelssen, M. (2017). Four Reasons Why Assisted Dying Should Not Be Offered for Depression. *Journal of Bioethical Inquiry* **14**, 151-157.
Bolt, E. E., Snijdewind, M. C., Willems, D. L., van der Heide, A. & Onwuteaka-Philipsen, B. D. (2015). Can physicians conceive of performing euthanasia in case of psychiatric disease, dementia or being tired of living? *Journal Medical Ethics* **41**, 592-8.
Broome, M. R. & de Cates, A. (2015). Choosing death in depression: a commentary on 'Treatment-resistant major depressive disorder and assisted dying'. *Journal Medical Ethics* **41**, 586-587.
Brothers of Charity (2017). Visie van de groep Broeders van Liefde in Belgie op euthanasie bij psychisch lijden in een niet-terminale situatie.

https://www.broedersvanliefde.be/nieuwsberichten/visie-euthanasie-bijgestuurd (Accessed Dec 2018).
Brown, S., Rittenbach, K., Cheung, S., McKean, G., Macmaster, F. P. & Clement, F. (2019). Current and Common Definitions of Treatment-Resistant Depression: Findings from a Systematic Review and Qualitative Interviews. *The Canadian Journal of Psychiatry* **64**, 380-387.
Bruns, F., Blumenthal, S. & Hohendorf, G. (2016). [Assisted suicide in Germany: medical diagnoses and personal reasons of 117 decedents]. *Deutsche Medizinische Wohenschrift* **141**, e32-7.
Bryden, J. (2021). Government agrees mentally ill should have access to assisted dying — in 2 years. In *CBC News* (Accessed Feb 2021).
Buchanan, A. E. & Brock, D. W. (1989). *Deciding for Others: The Ethics of Surrogate Decision Making*. Cambridge University Press Cambridge, UK.
Calkins, B. C. & Swetz, K. M. (2019). Physician Aid-in-Dying and Suicide Prevention in Psychiatry: A Moral Imperative Over a Crisis. *American Journal of Bioethics* **19**, 68-70.
Campbell, C. S. (2019). The Unbearable Burden of Suffering: Moral Crisis or Structural Failure? . *American Journal of Bioethics* **19**, 46-47.
Canetto, S. S. (2008). Women and suicidal behavior: a cultural analysis. *American Journal of Orthopsychiatry* **78**, 259-66.
Canetto, S. S. (2019). If physician-assisted suicide is the modern woman's last powerful choice, why are White women its leading advocates and main users? *Professional Psychology: Research and Practice* **50**, 39-50.
Canetto, S. S. & Sakinofsky, I. (1998). The gender paradox in suicide. *Suicide Life Threatening Behavior* **28**, 1-23.
Carrillo, F., Sigman, M., Fernández Slezak, D., Ashton, P., Fitzgerald, L., Stroud, J., Nutt, D. J. & Carhart-Harris, R. L. (2018). Natural speech algorithm applied to baseline interview data can predict which patients will respond to psilocybin for treatment-resistant depression. *Journal of Affective Disorders* **230**, 84-86.
CCA (2018). Council of Canadian Academies. The State of Knowledge on Medical Assistance in Dying Where a Mental Disorder is the Sole Underlying Medical Condition. https://cca-reports.ca/wp-content/uploads/2018/12/The-State-of-Knowledge-on-Medical-Assistance-in-Dying-Where-a-Mental-Disorder-is-the-Sole-Underlying-Medical-Condition.pdf.Ottawa, Canada (Accessed Jan 2019).
Cepeda, M. S., Reps, J., Fife, D., Blacketer, C., Stang, P. & Ryan, P. (2018). Finding treatment-resistant depression in real-world data: How a data-driven approach compares with expert-based heuristics. *Depression Anxiety* **35**, 220-228.
Chang, B., Choi, Y., Jeon, M., Lee, J., Han, K. M., Kim, A., Ham, B. J. & Kang, J. (2019). ARPNet: Antidepressant Response Prediction Network for Major Depressive Disorder. *Genes (Basel)* **10**.
Charlton, J. I. (1998). *Nothing About Us Without Us: Disability Oppression and Empowerment*. University of California Press.
Chekroud, A. M., Zotti, R. J., Shehzad, Z., Gueorguieva, R., Johnson, M. K., Trivedi, M. H., Cannon, T. D., Krystal, J. H. & Corlett, P. R. (2016). Cross-trial prediction of treatment outcome in depression: a machine learning approach. *The Lancet Psychiatry* **3**, 243-250.
Cheng (2019). Europe's top rights court to hear Belgian euthanasia case. In *Associated Press* (London).

Cholbi, M. J. (2013). The terminal, the futile, and the psychiatrically disordered. *International Journal of Law and Psychiatry* **36**, 498-505.
Claes, S., Van Bouwel, L., Haekens, A., Eneman, M., Otte, G., De Lepeleire, J., Calmeyn, M., Bazan, A. & Lemmens, W. (2015). Euthanasia for psychiatric patients: ethical and legal concerns about the Belgian practice. *British Medical Journal Open*.
Cohen, Z. D. & DeRubeis, R. J. (2018). Treatment Selection in Depression. *Annual Review Clinical Psychology* **14**, 209-236.
Conner, A., Azrael, D. & Miller, M. (2019). Suicide Case-Fatality Rates in the United States, 2007 to 2014. *Annals of Internal Medicine* **171**, 885.
Cooper, R. (2014). *Psychiatry and Philosophy of Science* Routledge (Taylor and Francis). New York, USA.
Cosgrove, L., Naudet, F., Hiogberg, G., Shaughnessy, A. & Cristea, I. A. (2020). Reconceptualising treatment-resistant depression as difficult-to-treat depression. *Lancet Psychiatry* **8**,11-13.
Cowley, C. (2013). Euthanasia in psychiatry can never be justified. A reply to Wijsbek. *Theoretical medicine and bioethics* **34**, 227-238.
Cowley, C. (2015). Commentary on 'Treatment-resistant major depressive disorder and assisted dying'. *Journal of Medical Ethics* **41**, 585-586.
Creighton, C., Cerel, J. & Battin, M. (2017). Statement of the American Association of Suicidology: "Suicide" is not the same as "Physician aid in dying". https://suicidology.org/wp-content/uploads/2019/07/AAS-PAD-Statement-Approved-10.30.17-ed-10-30-17.pdf (Accessed Dec 2018).
Cristea, I. A., Gentili, C., Cotet, C. D., Palomba, D., Barbui, C. & Cuijpers, P. (2017). Efficacy of Psychotherapies for Borderline Personality Disorder: A Systematic Review and Meta-analysis. *JAMA Psychiatry* **74**, 319-328.
Crossley, N. A., Scott, J., Ellison-Wright, I. & Mechelli, A. (2015). Neuroimaging distinction between neurological and psychiatric disorders. *British Journal of Psychiatry* **207**, 429-434.
Dahlen, E. R. & Canetto, S. S. (2002). The role of gender and suicide precipitant in attitudes toward nonfatal suicide behavior. *Death Studies* **26**, 99-116.
Day, M. (2018). Three Belgian doctors are investigated over euthanasia of woman with Asperger's. *British Medical Journal* **363**, k5106.
De Carlo, V., Calati, R. & Serretti, A. (2016). Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: A systematic review. *Psychiatry Research* **240**, 421-430.
De Hert, M., Van Bos, L., Sweers, K., Wampers, M., De Lepeleire, J. & Correll, C. U. (2015). Attitudes of Psychiatric Nurses about the Request for Euthanasia on the Basis of Unbearable Mental Suffering (UMS). *PLoS One* **10(12)**, e0144749.
De Standaard (2015). Euthanasiezaak voor het eerst aan Justitie doorgespeeld. In *De Standaard*.
De Vries, R. G. (2019). Moralities of method: Putting normative arguments in their (social and cultural) place. *American Journal of Bioethics* **19**, 40-42.
Decorte, I., Verfaillie, F., Moureau, L., Meynendonckx, S., Van Ballaer, K., De Geest, I. & Liégeois, A. (2020). Oyster Care: An Innovative Palliative Approach towards SPMI Patients. *Frontiers in Psychiatry* **11**, 509.

Dembo, J., Schuklenk, U. & Reggler, J. (2018). "For Their Own Good": A Response to Popular Arguments Against Permitting Medical Assistance in Dying (MAID) where Mental Illness Is the Sole Underlying Condition. *Canadian Journal of Psychiatry* **63**, 451-456.
Dembo, J. S. (2010). Addressing treatment futility and assisted suicide in psychiatry. *Journal of Ethics in Mental Health* **5**, 1-3.
Demyttenaere, K. (2019). What is treatment resistance in psychiatry? A "difficult to treat" concept. *World Psychiatry* **18**, 354-355.
Demyttenaere, K. & Van Duppen, Z. (2019). The Impact of (the Concept of) Treatment-Resistant Depression: An Opinion Review. *International Journal of Neuropsychopharmacology* **22**, 85-92.
den Hartogh, G. (2015). Why extra caution is needed in the case of depressed patients. *Journal of Medical Ethics* **41**, 588-589.
den Hartogh, G. (2016). Two Kinds of Suicide. *Bioethics* **30**, 672-680.
den Hartogh, G. (2017). Stervenshulp holt zolgvuldigheidseisen uit. In *Medisch Contact*.
den Hartogh, G. (2019). Why normative judgment is inescapable. *American Journal of Bioethics* **19**, 48-50.
DeRubeis, R. J. (2019). The history, current status, and possible future of precision mental health. *Behav Res Ther* **123**, 103506.
Dierickx, S., Deliens, L., Cohen, J. & Chambaere, K. (2016). Euthanasia in Belgium: trends in reported cases between 2003 and 2013. *Canadian Medical Association Journal* **188**, E407-e414.
Dierickx, S., Deliens, L., Cohen, J. & Chambaere, K. (2017). Euthanasia for people with psychiatric disorders or dementia in Belgium: analysis of officially reported cases. *BMC Psychiatry* **17**, 203.
Dinga, R., Marquand, A. F., Veltman, D. J., Beekman, A. T. F., Schoevers, R. A., Van Hemert, A. M., Penninx, B. W. J. H. & Schmaal, L. (2018). Predicting the naturalistic course of depression from a wide range of clinical, psychological, and biological data: a machine learning approach. *Translational Psychiatry* **8**, 241.
Doernberg, S. N., Peteet, J. R. & Kim, S. Y. (2016). Capacity Evaluations of Psychiatric Patients Requesting Assisted Death in the Netherlands. *Psychosomatics* **57**, 556-565.
Dom, G. (2015). [Do you know the CRPD? (Convention on the Rights of Persons with Disabilities)]. *Tijdschrift voor Psychiatrie* **57**, 158-60.
Downar, J., Fowler, R. A., Halko, R., Huyer, L. D., Hill, A. D. & Gibson, J. L. (2020). Early experience with medical assistance in dying in Ontario, Canada: a cohort study. *Canadian Medical Association Journal* **192**, E173-E181.
Dunner, D. L., Rush, A. J., Russell, J. M., Burke, M., Woodard, S., Wingard, P. & Allen, J. (2006). Prospective, Long-Term, Multicenter Study of the Naturalistic Outcomes of Patients With Treatment-Resistant Depression. *Journal of Clinical Psychiatry* **67**, 688-695.
Dutch Act (2002). Wet toetsing levensbeëindiging op verzoek en hulp bij zelfdoding. Available at: https://wetten.overheid.nl/BWBR0012410/2020-03-19. An English translation of the due care criteria set out in the Act can be found in: EuthanasiaCode, 2018 (p.8).
Dworkin, R., Nagel, T., Nozick, R., Rawls, J. & Thompson, J. J. (1997). Assisted Suicide: The Philosophers' Brief. *The New York Review of Books*.
Elo, S. & Kyngas, H. (2008). The qualitative content analysis process. *Journal of Advance Nursing* **62**, 107-15.

EuthanasiaCode (2018). Review Procedures in Practice. https://english.euthanasiecommissie.nl/the-committees/code-of-practice. Regional Euthanasia Review Committees (Accessed June 2018).
Evenblij, K., Pasman, H. R. W., Pronk, R. & Onwuteaka-Philipsen, B. D. (2019). Euthanasia and physician-assisted suicide in patients suffering from psychiatric disorders: a cross-sectional study exploring the experiences of Dutch psychiatrists. *BMC Psychiatry* **19,** 74.
FCECE (2020). Federal Control and Evaluation Commission for Euthanasia. Negende verslag aan de wetgevende kamers (2018-2019) https://overlegorganen.gezondheid.belgie.be/sites/default/files/documents/9_euthanasie-verslag_2018-2019-nl.pdf. (Accessed December 2020).
Fekadu, A., Rane, L. J., Wooderson, S. C., Markopoulou, K., Poon, L. & Cleare, A. J. (2012). Prediction of longer-term outcome of treatment-resistant depression in tertiary care. *British Journal of Psychiatry* **201**, 369-375.
Fekadu, A., Wooderson, S. C., Markopoulo, K., Donaldson, C., Papadopoulos, A. & Cleare, A. J. (2009). What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. *Journal of Affective Disorders* **116**, 4-11.
Fekadu, A., Wooderson, S. C., Rane, L. J., Markopoulou, K., Poon, L. & Cleare, A. J. (2011). Long-Term Impact of Residual Symptoms in Treatment-Resistant Depression. *The Canadian Journal of Psychiatry* **56**, 549-557.
Foster, C. (2019). Kious and Battin's dilemma resolved: outlaw Physician-Aid- in Dying. *American Journal of Bioethics* **19**, 50-51.
Franklin, J. C., Hessel, E. T. & Prinstein, M. J. (2011). Clarifying the role of pain tolerance in suicidal capability. *Psychiatry Research* **189**, 362-7.
Freeman, M. C., Kolappa, K., de Almeida, J. M., Kleinman, A., Makhashvili, N., Phakathi, S., Saraceno, B. & Thornicroft, G. (2015). Reversing hard won victories in the name of human rights: a critique of the General Comment on Article 12 of the UN Convention on the Rights of Persons with Disabilities. *Lancet Psychiatry* **2**, 844-50.
Friesen, P. (2020). Medically Assisted Dying and Suicide: How Are They Different, and How Are They Similar? *Hastings Center Report* **50**, 32-43.
Gaignard, M. E. & Hurst, S. (2019). A qualitative study on existential suffering and assisted suicide in Switzerland. *BMC Med Ethics* **20**, 34.
Gaind, K. S. (2020). What Does "Irremediability" in Mental Illness Mean? *Canadian Journal of Psychiatry* **65**, 604-606.
Gardner, C. & Kleinman, A. (2019). Medicine and the Mind - The Consequences of Psychiatry's Identity Crisis. *New England Journal of Medicine* **381**, 1697-1699.
Garg, R. (2020). Austria Constitutional Court strikes down ban on assisted death In *Jurist (Legal News and Commentary) https://www.canada.ca/en/health-canada/services/medical-assistance-dying.html* (Accessed Jan 2021)
Gastmans, C. (2018). Ethisch advies 20: Levenseindezorg voor niet-terminale patiënten met ernstige psychiatrische aandoeningen https://www.zorgneticuro.be/publicaties/ethisch-advies-20-levenseindezorg-voor-niet-terminale-pati%C3%ABnten-met-ernstige. Zorgnet-Icuro, Brussel (Accessed March 2019).
Gather, J. (2020). Übersicht über ethische Argumente. *Info Neurologie & Psychiatrie* **22,** 10.

Gaynes, B. N., Lux, L., Gartlehner, G., Asher, G., Forman-Hoffman, V., Green, J., Boland, E., Weber, R. P., Randolph, C., Bann, C., Coker-Schwimmer, E., Viswanathan, M. & Lohr, K. N. (2020). Defining treatment-resistant depression. *Depression and Anxiety* **37**, 134-145.
Ge, R., Blumberger, D. M., Downar, J., Daskalakis, Z. J., Dipinto, A. A., Tham, J. C. W., Lam, R. & Vila-Rodriguez, F. (2017). Abnormal functional connectivity within resting-state networks is related to rTMS-based therapy effects of treatment resistant depression: A pilot study. *Journal of Affective Disorders* **218**, 75-81.
Gillan, C. M. & Whelan, R. (2017). What big data can do for treatment in psychiatry. *Current Opinion in Behavioral Sciences* **18**, 34-42.
Giourou, E., Skokou, M., Andrew, S. P., Alexopoulou, K., Gourzis, P. & Jelastopulu, E. (2018). Complex posttraumatic stress disorder: The need to consolidate a distinct clinical syndrome or to reevaluate features of psychiatric disorders following interpersonal trauma? *World Journal of Psychiatry* **8**, 12-19.
Graneheim, U. H. & Lundman, B. (2004). Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today* **24**, 105-12.
Griffith, J., Weyers, H. & Adams, M. (2008). *Euthanasia and Law in Europe*. Hart Publishing: Portland, OR.
Grisso, T. & Appelbaum, P. S. (1998). *Assessing competence to consent to treatment: A guide for physicians and other health professionals*. Oxford University Press: New York, US.
Groenewoud, J. H., Van Der Heide, A., Tholen, A. J., Schudel, W. J., Hengeveld, M. W., Onwuteaka-Philipsen, B. D., Van Der Maas, P. J. & Van Der Wal, G. (2004). Psychiatric consultation with regard to requests for euthanasia or physician-assisted suicide. *General Hospital Psychiatry* **26**, 323-30.
Groenewoud, J. H., van der Maas, P. J., van der Wal, G., Hengeveld, M. W., Tholen, A. J., Schudel, W. J. & van der Heide, A. (1997). Physician-assisted death in psychiatric practice in the Netherlands. *New England Journal of Medicine* **336**, 1795-801.
Grove, W. M., Zald, D. H., Lebow, B. S., Snitz, B. E. & Nelson, C. (2000). Clinical versus mechanical prediction: a meta-analysis. *Psychological Assessment* **12**, 19-30.
Haekens, A., Calmeyn, M., Lemmens, W., Pollefeyt, D. & Bazan, A. (2017). Mogen we nu (eindelijk) vragen stellen over euthanasie bij psychisch lijden? In *VRT Nieuws*.
Hamilton, N. G., Edwards, P. J., Boehnlein, J. K. & Hamilton, C. A. (1998). The doctor-patient relationship and assisted suicide: a contribution from dynamic psychiatry. *American Journal of Forensic Psychiatry* **19**, 59-75.
Hatherley, J. J. (2019). Is the exclusion of psychiatric patients from access to physician-assisted suicide discriminatory? *Journal of Medical Ethics* **45**, 817-820.
Hawkins, J. & Charland, L. (2020). Decision-making capacity. In *Stanford Encyclopedia of Philosophy*. https://plato.stanford.edu/entries/decision-capacity (Accessed Dec 2020)
Hawton, K. (2000). Sex and suicide. Gender differences in suicidal behaviour. *British Journal of Psychiatry* **177**, 484-5.
Hedberg, K. & New, C. (2017). Oregon's Death With Dignity Act: 20 Years of Experience to Inform the Debate. *Ann Intern Med* **167**, 579-583.
Hirsch, J. (2016). The Wish to Die: Assisted Suicide and Mental Illness. *Journal of Social Work in End-of-life & Palliative Care* **12**, 231-235.

Ho & Norman (2019). Social Determinants of Mental Health and Physician Aid-in-Dying: The Real Moral Crisis. *American Journal of Bioethics* **19**, 52-54.
Horn, R. (2020). The right to a self-determined death as expression of the right to freedom of personal development: The German Constitutional Court takes a clear stand on assisted suicide. *Journal of Medical Ethics* **46**, 416-417.
Hosseini, M., Powell, M., Collins, J., Callahan-Flintoft, C., Jones, W., Bowman, H. & Wyble, B. (2020). I tried a bunch of things: The dangers of unexpected overfitting in classification of brain data. *Neuroscience & Biobehavior Review* **119**, 456-467.
Hsieh, H. F. & Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qualitative Health Research* **15**, 1277-88.
Huisman (2017). Levenseindekliniek kan de vraag niet aan en zoekt tientallen nieuwe artsen. In *De Volkskrant* (Accessed Dec 8, 2018)
Hurst, S. A. & Mauron, A. (2017). Assisted Suicide in Switzerland: Clarifying Liberties and Claims. *Bioethics* **31**, 199-208.
Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C. & Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry* **167**, 748-51.
Isometsa, E. T. & Lonnqvist, J. K. (1998). Suicide attempts preceding completed suicide. *British Jorunal of Psychiatry* **173**, 531-5.
Jacobucci, R., Littlefield, A. K., Millner, A. J., Kleiman, E. M. & Steinley, D. (2020). Pairing machine learning and clinical psychology: how you evaluate predictive performance matters. *PsyArXiv*, 1-36.
Jansen, L. A., Wall, S. & Miller, F. G. (2019). Drawing the line on physician-assisted death. *Journal of Medical Ethics* **45**, 190-197.
Jones, D. A. (2011). Is There a Logical Slippery Slope from Voluntary to Nonvoluntary Euthanasia? *Kennedy Institute of Ethics Journal* **21**, 379-404.
Jones, D. A., Gastmans, C. & MacKellar, C. (2017). Euthanasia and Assisted Suicide: Lessons from Belgium. Cambridge University Press (Cambridge, UK).
Kautzky, A., Baldinger, P., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., Serretti, A., Lanzenberger, R. & Kasper, S. (2015). The combined effect of genetic polymorphisms and clinical parameters on treatment outcome in treatment-resistant depression. *European Neuropsychopharmacology* **25**, 441-53.
Kautzky, A., Baldinger-Melich, P., Kranz, G. S., Vanicek, T., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., Serretti, A., Lanzenberger, R. & Kasper, S. (2017). A New Prediction Model for Evaluating Treatment-Resistant Depression. *Journal Clinical Psychiatry* **78**, 215-222.
Kautzky, A., Dold, M., Bartova, L., Spies, M., Kranz, G. S., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., Fabbri, C., Serretti, A., Lanzenberger, R., Dikeos, D., Rujescu, D. & Kasper, S. (2019). Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. *Acta Psychiatrica Scandinavica* **139**, 78-88.
Kautzky, A., Dold, M., Bartova, L., Spies, M., Vanicek, T., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., Fabbri, C., Serretti, A., Lanzenberger, R. & Kasper, S. (2018). Refining Prediction in Treatment-Resistant Depression: Results of Machine Learning Analyses in the TRD III Sample. *Journal Clinical Psychiatry* **79**.

Kelly, B. D. (2014). An end to psychiatric detention? Implications of the United Nations Convention on the Rights of Persons with Disabilities. *British Journal of Psychiatry* **204**, 174-175.
Kelly, B. D. (2017). Invited commentary on ... When unbearable suffering incites psychiatric patients to request euthanasia. *British Journal of Psychiatry* **211**, 248-249.
Kelly, B. D. & McLoughlin, D. M. (2002). Euthanasia, assisted suicide and psychiatry: A Pandora's box. *British Journal of Psychiatry* **181**, 278-279.
Kendell, R. E. (2001). The distinction between mental and physical illness. *British Journal of Psychiatry* **178**, 490-3.
Kendler, K. S. (2019). From Many to One to Many-the Search for Causes of Psychiatric Illness. *JAMA Psychiatry **76**,* 1085-1091.
Kendler, K. S., Zachar, P. & Craver, C. (2011). What kinds of things are psychiatric disorders? *Psychological Medicine* **41**, 1143-1150.
Keown, J. (2002). *Euthanasia, Ethics and Public Policy*. Cambridge University Press (Cambridge, UK).
Khodayari-Rostamabad, A., Reilly, J. P., Hasey, G. M., de Bruin, H. & Maccrimmon, D. J. (2013). A machine learning approach using EEG data to predict response to SSRI treatment for major depressive disorder. *Clinical Neurophysiology* **124**, 1975-85.
Kim, S. Y., De Vries, R. G. & Peteet, J. R. (2016). Euthanasia and Assisted Suicide of Patients With Psychiatric Disorders in the Netherlands 2011 to 2014. *JAMA Psychiatry* **73**, 362-8.
Kim, S. Y. & Lemmens, T. (2016). Should assisted dying for psychiatric disorders be legalized in Canada? *Canadian Medical Association journal* **188**, E337-E339.
Kim, S. Y. H. (2016a). Capacity assessments as a safeguards for psychiatric patients requesting euthanasia. *Journal of Ethics in Mental Health* (Open Volume on Medical Assistance in Dying)
Kim, S. Y. H. (2016b). The Place of Ability to Value in the Evaluation of Decision-Making Capacity. In *Philosophy and Psychiatry: Problems, Intersections and New Perspectives.* (ed. Moseley and Gala). Routledge, New York.
Kim, S. Y. H. (2019). Lives Not Worth Living in Modern Euthanasia Regimes. *Journal of Policy and Practice in Intellectual Disabilities* **16**, 134-136.
Kim, S. Y. H., Conwell, Y. & Caine, E. D. (2018). Suicide and Physician-Assisted Death for Persons With Psychiatric Disorders: How Much Overlap? *JAMA Psychiatry* **75**, 1099-1100.
Kious, B. M. & Battin, M. P. (2019). Physician Aid-in-Dying and Suicide Prevention in Psychiatry: A Moral Crisis? *American Journal of Bioethics* **19**, 29-39.
Kissane, D. W. & Kelly, B. J. (2000). Demoralisation, depression and desire for death: problems with the Dutch guidelines for euthanasia of the mentally ill. *Australian & New Zealand Journal of Psychiatry* **34**, 325-333.
Klonsky, E. D., May, A. M. & Saffer, B. Y. (2016). Suicide, Suicide Attempts, and Suicidal Ideation. *Annual Review of Clinical Psychology* **12**, 307-330.
Klonsky, E. D., Saffer, B. Y. & Bryan, C. J. (2018). Ideation-to-action theories of suicide: a conceptual and empirical update. *Current Opinion in Psychology* **22**, 38-43.
Kurniawan, C. & van der Zwaard, R. (2018). Euthanasie bij psychiatrie roept vragen op. https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/euthanasie-bij-psychiatrie-roept-vragen-op.htm *Medisch Contact*. (Accessed Apr 2018)
Kvarstein, E. H., Pedersen, G., Folmo, E., Urnes, O., Johansen, M. S., Hummelen, B., Wilberg, T. & Karterud, S. (2019). Mentalization-based treatment or psychodynamic treatment

programmes for patients with borderline personality disorder - the impact of clinical severity. *Psychology and psychotherapy*.**92**, 91-111.
Le Glaz, A., Berrouiguet, S., Deok-Hee, K., Walter, M. & Lemey, C. (2019). Euthanasia for mental suffering reduces stigmatization but may lead to an extension of this practice without safeguards. *American Journal of Bioethics* **19**, 57-59.
Leamy, M., Bird, V., Boutillier, C. L., Williams, J. & Slade, M. (2011). Conceptual framework for personal recovery in mental health: systematic review and narrative synthesis. *British Journal of Psychiatry* **199**, 445-452.
Leichsenring, F. & Leibing, E. (2003). The effectiveness of psychodynamic therapy and cognitive behavior therapy in the treatment of personality disorders: a meta-analysis. *American Journal of Psychiatry* **160**, 1223-32.
Lemmens, T., Kim, H. & Kurz, E. (2018). Why Canada's Medical Assistance in Dying Legislation Should Be C(h)arter Compliant and What It May Help to Avoid. *McGill Journal of Law and Health (Revue de Droit et Santé de McGill)* **11**, S61-S148.
Lemmens, T. (2019). When a theoretical commitment to broad Physician-Aid-in-Dying faces the reality of its implementation. *American Journal of Bioethics* **19**, 65-68.
Levenseindekliniek (2018). http://www.levenseindekliniek.nl. (Accessed May 2018)
Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., Clarke, M., Devereaux, P. J., Kleijnen, J. & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *British Medical Journal* **339**, b2700.
Linehan, M. M., Comtois, K. A., Murray, A. M., Brown, M. Z., Gallop, R. J., Heard, H. L., Korslund, K. E., Tutek, D. A., Reynolds, S. K. & Lindenboim, N. (2006). Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. *Archives Geneneral Psychiatry* **63**, 757-66.
Linehan, M. M., Tutek, D. A., Heard, H. L. & Armstrong, H. E. (1994). Interpersonal outcome of cognitive behavioral treatment for chronically suicidal borderline patients. *American Journal of Psychiatry* **151**, 1771-6.
Malhi, G. S. & Byrow, Y. (2016). Is treatment-resistant depression a useful concept? *Evidence Based Mental Health* **19**, 1-3.
McAllister-Williams, R. H., Arango, C., Blier, P., Demyttenaere, K., Falkai, P., Gorwood, P., Hopwood, M., Javed, A., Kasper, S., Malhi, G. S., Soares, J. C., Vieta, E., Young, A. H., Papadopoulos, A. & Rush, A. J. (2020). The identification, assessment and management of difficult-to-treat depression: An international consensus statement. *Journal of Affective Disorders* **267**, 264-282.
McCullough, L. B., Coverdale, J. H. & Chervenak, F. A. (2007). Constructing a systematic review for argument-based clinical ethics literature: the example of concealed medications. *Journal of Medicine and Philosophy* **32**, 65-76.
McDougall, R. (2014). Systematic reviews in bioethics: types, challenges, and value. *Journal of Medicine and Philosophy* **39**, 89-97.
McIntyre, R. S., Filteau, M. J., Martin, L., Patry, S., Carvalho, A., Cha, D. S., Barakat, M. & Miguelez, M. (2014). Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *Journal of Affective Disorders* **156**, 1-7.

McMain, S. F., Links, P. S., Gnam, W. H., Guimond, T., Cardish, R. J., Korman, L. & Streiner, D. L. (2009). A randomized trial of dialectical behavior therapy versus general psychiatric management for borderline personality disorder. *American Journal of Psychiatry* **166**, 1365-74.
Mergl, R., Koburger, N., Heinrichs, K., Székely, A., Tóth, M. D., Coyne, J., Quintão, S., Arensman, E., Coffey, C., Maxwell, M., Värnik, A., Van Audenhove, C., McDaid, D., Sarchiapone, M., Schmidtke, A., Genz, A., Gusmão, R. & Hegerl, U. (2015). What Are Reasons for the Large Gender Differences in the Lethality of Suicidal Acts? An Epidemiological Analysis in Four European Countries. *PLOS One* **10**, e0129062.
Mertz, M., Strech, D. & Kahrass, H. (2017). What methods do reviews of normative ethics literature use for search, selection, analysis, and synthesis? In-depth results from a systematic review of reviews. *Systematic Reviews* **6**, 261.
Meuldijk, D., McCarthy, A., Bourke, M. E. & Grenyer, B. F. (2017). The value of psychological treatment for borderline personality disorder: Systematic review and cost offset analysis of economic evaluations. *PLoS One* **12**, e0171592.
Micoulaud-Franchi, J. A., Richieri, R., Cermolacce, M., Loundou, A., Lancon, C. & Vion-Dury, J. (2012). Parieto-temporal alpha EEG band power at baseline as a predictor of antidepressant treatment response with repetitive Transcranial Magnetic Stimulation: a preliminary study. *Journal of Affective Disorders* **137**, 156-60.
Miller, D. G. & Kim, S. Y. H. (2017). Euthanasia and physician-assisted suicide not meeting due care criteria in the Netherlands: a qualitative review of review committee judgements. *British Medical Journal Open* **7**, e017628-2017-017628.
Miller, F. G. (2015). Treatment-Resistant Depression and Physician-Assisted Death. *Journal of Medical Ethics: The Journal of the Institute of Medical Ethics* **41**, 885-886.
Miller, F. G. (2019). Physician-Assisted Death and Journalism Ethics. The Hastings Center Bioethics Forum (Accessed Dec 10, 2019)
Miller, F. G. & Appelbaum, P. S. (2018). Physician-Assisted Death for Psychiatric Patients - Misguided Public Policy. *New England Jorunal of Medicine* **378**, 883-885.
Minelli, A., Abate, M., Zampieri, E., Gainelli, G., Trabucchi, L., Segala, M., Sartori, R., Gennarelli, M., Conca, A. & Bortolomasi, M. (2016). Seizure Adequacy Markers and the Prediction of Electroconvulsive Therapy Response. *Journal of ECT* **32**, 88-92.
Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* **6**, e1000097.
Möller, H.-J. (2020). The ongoing discussion on termination of life on request. A review from a German/European perspective. *International Journal of Psychiatry in Clinical Practice*, 1-17.
Naudts, K., Ducatelle, C., Kovacs, J., Laurens, K., Van Den Eynde, F. & Van Heeringen, C. (2006). Euthanasia: The role of the psychiatrist. *British Journal of Psychiatry* **188**, 405-409.
Newton-Howes, G., Tyrer, P., Johnson, T., Mulder, R., Kool, S., Dekker, J. & Schoevers, R. (2014). Influence of personality on the outcome of treatment in depression: systematic review and meta-analysis. *Journal of Personality Disorders* **28**, 577-93.
Ng, C. H., Kato, T., Han, C., Wang, G., Trivedi, M., Ramesh, V., Shao, D., Gala, S., Narayanan, S., Tan, W., Feng, Y. & Kasper, S. (2019). Definition of treatment-resistant depression - Asia Pacific perspectives. *Journal of Affective Disorders* **245**, 626-636.

Nicolini, M. E., Kim, S. Y. H., Churchill, M. E. & Gastmans, C. (2020a). Should euthanasia and assisted suicide for psychiatric disorders be permitted? A systematic review of reasons. *Psychological Medicine* **50**, 1241-1256.
Nicolini, M. E., Peteet, J. R., Donovan, G. K. & Kim, S. Y. H. (2020b). Euthanasia and assisted suicide of persons with psychiatric disorders: the challenge of personality disorders. *Psychological Medicine* **50**, 575-582.
Nie, Z., Vairavan, S., Narayan, V. A., Ye, J. & Li, Q. S. (2018). Predictive modeling of treatment resistant depression using data from STAR*D and an independent clinical study. *PLoS One* **13**, e0197268.
Nock, M. K., Hwang, I., Sampson, N. A. & Kessler, R. C. (2010). Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. *Molecular Psychiatry* **15**, 868-76.
NVVP (2018). Nederlanse Vereniging voor Psychiatrie. Levensbeëindiging op verzoek bij patiënten met een psychische stoornis. https://richtlijnendatabase.nl/richtlijn/levensbeeindiging_op_verzoek_psychiatrie/startpagina_-_levensbe_indiging_op_verzoek.html (Accessed June 2019).
Nys, H. (2017). A discussion of the legal rules on euthanasia in Belgium briefly compared with the rules in Luxembourg and the Netherlands. pp. 7-25. In *Euthanasia and Assisted Suicide. Lessons from Belgium.* (ed. D. A. Jones, C. Gastmans and C. MacKellar). Cambridge University Press: Cambridge, UK.
O'Connor, R. C. & Nock, M. K. (2014). The psychology of suicidal behaviour. *Lancet Psychiatry* **1**, 73-85.
O'Connor, R. C., Wetherall, K., Cleare, S., Eschle, S., Drummond, J., Ferguson, E., O'Connor, D. B. & O'Carroll, R. E. (2018). Suicide attempts and non-suicidal self-harm: national prevalence study of young adults. *British Journal of Psychiatry Open* **4**, 142-148.
Oldham, J., Gabbard, G., Goin, M., Gunderson, J., Soloff, P., Spiegel, D., Stone, M. & Phillips, K. (2010). American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients With Borderline Personality Disorder. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bpd.pdf (Accessed Sept 2018)
Oldham, J. M. (2006). Borderline personality disorder and suicidality. *The American Journal of Psychiatry* **163**, 20-26.
Olié, E. & Courtet, P. (2016). The controversial issue of euthanasia in patients with psychiatric illness. *Journal of the American Medical Association* **316**, 656-657.
Onwuteaka-Philipsen, B. D., Legemaate, J., van Der Heide, A., van Delden, H., Evenblij, K., El Hammoud, I., Pasman, R., Ploem, C., Pronk, R., van de Vathorst, S. & Willems, D. (2017). Derde evaluatie Wet toesting levensbeeindiging op verzoek en hulp bij zelfdoding (*Third Evaluation of the Dutch Terminatin of Life on Request and Assisted Suicide Act*). Den Haag, The Netherlands.
Oram, S., Khalifeh, H. & Howard, L. M. (2017). Violence against women and mental health. *The Lancet Psychiatry* **4**, 159-170.
Orde der Artsen (2019). Deontologische richtlijnen voor de toepassing van euthanasie bij patiënten die psychisch lijden ten gevolge van een psychiatrische aandoening. https://www.ordomedic.be/nl/adviezen/advies/deontologische-richtlijnen-voor-de-toepassing-

van-euthanasie-bij-patienten-die-psychisch-lijden-ten-gevolge-van-een-psychiatrische-aandoening (Accessed May 2019).
Owen, G. (2016). Commentary on "Decision-Making Capacity to Consent to Medical Assistance in Dying for Persons with Mental Disorders". *Journal of Ethics in Mental Health* Open Volume on Medical Assistance in Dying.
Owen, G. S., Richardson, G., David, A. S., Szmukler, G., Hayward, P. & Hotopf, M. (2008). Mental capacity to make decisions on treatment in people admitted to psychiatric hospitals: cross sectional study. *British Medical Jorunal* **337**, a448.
Pandarakalam, J. P. (2108). Challenges of Treatment-Resistant Depression. *Psychiatria Danubina* **30**, 273-284.
Parker, M. (2013). Defending the indefensible? Psychiatry, assisted suicide and human freedom. *International Journal of Law and Psychiatry* **36**, 485-97.
Pearce, S. (2017). Invited commentary on ... When unbearable suffering incites psychiatric patients to request euthanasia: a qualitative study. *British Journal of Psychiatry* **211**, 246-247.
Penninx, B. W., Beekman, A. T., Smit, J. H., Zitman, F. G., Nolen, W. A., Spinhoven, P., Cuijpers, P., De Jong, P. J., Van Marwijk, H. W., Assendelft, W. J., Van Der Meer, K., Verhaak, P., Wensing, M., De Graaf, R., Hoogendijk, W. J., Ormel, J. & Van Dyck, R. (2008). The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research* **17**, 121-40.
Perlis, R. H. (2013). A clinical risk stratification tool for predicting treatment resistance in major depressive disorder. *Biological Psychiatry* **74**, 7-14.
Perlis, R. H., Iosifescu, D. V., Castro, V. M., Murphy, S. N., Gainer, V. S., Minnier, J., Cai, T., Goryachev, S., Zeng, Q., Gallagher, P. J., Fava, M., Weilburg, J. B., Churchill, S. E., Kohane, I. S. & Smoller, J. W. (2012). Using electronic medical records to enable large-scale studies in psychiatry: treatment resistant depression as a model. *Psychological Medicine* **42**, 41-50.
Perna, G., Grassi, M., Caldirola, D. & Nemeroff, C. B. (2018). The revolution of personalized psychiatry: will technology make it happen sooner? *Psychological Medicine* **48**, 705-713.
Pinedo, D. (2018). Voor Aurelia was het leven een marteling. *NRC https://www.nrc.nl/nieuws/2018/02/10/voor-aurelia-was-het-leven-een-marteling-a1591735*.
Player, C. (2018). Death with dignity and mental disorder. *Arizona Law Review* **60**, 116-161.
Poldrack, R. A., Huckins, G. & Varoquaux, G. (2020). Establishment of Best Practices for Evidence for Prediction: A Review. *JAMA Psychiatry* **77**, 534-540.
Pronk, R., Evenblij, K., Willems, D. L. & van de Vathorst, S. (2019). Considerations by Dutch Psychiatrists Regarding Euthanasia and Physician-Assisted Suicide in Psychiatry: A Qualitative Study. *Journal Clinical Psychiatry* **80,** 19m12736.
Pronk, R., Willems, D. L. & Van De Vathorst, S. (2020). Do Doctors Differentiate Between Suicide and Physician-Assisted Death? A Qualitative Study into the Views of Psychiatrists and General Practitioners. *Culture, Medicine, and Psychiatry* (Online ahead of print Aug 2020: 10.1007/s11013-020-09686-2).
Provencher-Renaud, G., Larivée, S. & Sénéchal, C. (2019). Access to medical assistance in dying for people with mental disorders. *Annales Medico-Psychologiques* **117**, 801-808.
Raus, K., Vanderhaegen, B. & Sterckx, S. (2021). Euthanasia in Belgium: Shortcomings of the Law and Its Application and of the Monitoring of Practice. *Journal of Medicine and Philosophy* **46**, 80-107.

Reel, K. (2018). Denying Assisted Dying Where Death Is Not Reasonably Foreseeable: Intolerable Overgeneralization in Canadian End-of-Life Law. *Canadian Journal of Bioethics* **1**, 71-81.
Rhebergen, D., Lamers, F., Spijker, J., de Graaf, R., Beekman, A. T. & Penninx, B. W. (2012). Course trajectories of unipolar depressive disorders identified by latent class growth analysis. *Psychological Medicine* **42**, 1383-96.
Richieri, R., Boyer, L., Farisse, J., Colavolpe, C., Mundler, O., Lancon, C. & Guedj, E. (2011). Predictive value of brain perfusion SPECT for rTMS response in pharmacoresistant depression. *European Jorunal of Nuclear Medicine Molecular Imaging* **38**, 1715-22.
Rooney, W., Schuklenk, U. & van de Vathorst, S. (2018). Are Concerns About Irremediableness, Vulnerability, or Competence Sufficient to Justify Excluding All Psychiatric Patients from Medical Aid in Dying? *Health Care Analysis* **26**, 326-343.
Rousseau, S., Turner, S., Chochinov, H. M., Enns, M. W. & Sareen, J. (2017). A National Survey of Canadian Psychiatrists' Attitudes toward Medical Assistance in Death. *Canadian journal of psychiatry. Revue canadienne de psychiatrie* **62**, 787-794.
RTE (2014). Regional Euthanasia Review Committees Annual Report 2014. https://www.euthanasiecommissie.nl/de-toetsingscommissies/uitspraken/jaarverslagen/2014/nl/nl/jaarverslag-2014. The Hague, the Netherlands. (Accessed Dec 2018)
RTE (2017). Regional Euthanasia Review Committees Annual Report 2017. https://www.euthanasiecommissie.nl/de-toetsingscommissies/uitspraken/jaarverslagen/2017/mei/17/jaarverslag-2017. The Hague, the Netherlands (Accessed Dec 2018)
RTE (2018). Regional Euthanasia Review Committees Annual Report 2018. https://www.euthanasiecommissie.nl/de-toetsingscommissies/uitspraken/jaarverslagen/2018/april/11/jaarverslag-2018. The Hague, the Netherlands. (Accessed March 2019)
Ruhé, H. G., Van Rooijen, G., Spijker, J., Peeters, F. P. M. L. & Schene, A. H. (2012). Staging methods for treatment resistant depression. A systematic review. *Journal of Affective Disorders* **137**, 35-45.
Rukavina, S. (2019). Quebec judge overturns parts of federal, provincial laws on medically assisted dying. https://www.cbc.ca/news/canada/montreal/medically-assisted-dying-law-overturned-quebec-1.5279067. In *CBC Montreal*.
Rush, A. J., Aaronson, S. T. & Demyttenaere, K. (2019). Difficult-to-treat depression: A clinical and research roadmap for when remission is elusive. *Australian & New Zealand Journal of Psychiatry* **53**, 109-118.
Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J. & Fava, M. (2006). Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *American Journal of Psychiatry* **163**, 1905-1917.
Sackeim, H. A., Aaronson, S. T., Bunker, M. T., Conway, C. R., Demitrack, M. A., George, M. S., Prudic, J., Thase, M. E. & Rush, A. J. (2019). The assessment of resistance to antidepressant

treatment: Rationale for the Antidepressant Treatment History Form: Short Form (ATHF-SF). *Journal of Psychiatric Research* **113**, 125-136.
Sagan, A. (2015). Equal in the Presence of Death? *Journal of Medical Ethics: The Journal of the Institute of Medical Ethics* **41**, 584.
SAMS (2018). Management of dying and death (Swiss Academy of Medical Sciences). Bern, Switzerland.
Schaerlaken, J. (2020). De diagnose 'autisme' redde mijn leven. In *De Standaard*. https://www.standaard.be/cnt/dmf20200117_04810435 (Accessed Jan 2020)
Schoevers, R. A., Asmus, F. P. & Van Tilburg, W. (1998). Physician-assisted suicide in psychiatry: developments in the Netherlands. *Psychiatric Services* **49**, 1475-1480.
Schrijvers, D. L., Bollen, J. & Sabbe, B. G. (2012). The gender paradox in suicidal behavior and its impact on the suicidal process. *Journal of Affective Disorders* **138**, 19-26.
Schuklenk, U. (2019). Certainty is not a morally defensible threshold to determine eligibility for assisted dying. *Bioethics* **33**, 219-220.
Schuklenk, U. & van de Vathorst, S. (2015). Treatment-resistant major depressive disorder and assisted dying. *Journal of Medical Ethics* **41**, 577-583.
Schweitser, F., Stuy, J., Distelmans, W. & Rigo, A. (2020). Assessment of patient decision-making capacity in the context of voluntary euthanasia for psychic suffering caused by psychiatric disorders: a qualitative study of approaches among Belgian physicians. *Journal of Medical Ethics* (Online ahead of print).
Simpson, A. I. F. (2018). Medical Assistance in Dying and Mental Health: A Legal, Ethical, and Clinical Analysis. *Canadian Journal of Psychiatry.Revue canadienne de psychiatrie* **63**, 80-84.
Sinyor, M. & Schaffer, A. (2020). The Lack of Adequate Scientific Evidence Regarding Physician-assisted Death for People with Psychiatric Disorders Is a Danger to Patients. *Canadian Journal of Psychiatry. Revue canadienne de psychiatrie.* **65**, 607-609.
Smith, D. H. (2020). Medical Assistance in Dying. A Review of Court Decisions on the issue of MAiD and Psychiatric Illness. *The Canadian Journal of Psychiatry*. *Revue canadienne de psychiatrie.* **65**, 610-611.
Snijdewind, M. C., Willems, D. L., Deliens, L., Onwuteaka-Philipsen, B. D. & Chambaere, K. (2015). A Study of the First Year of the End-of-Life Clinic for Physician-Assisted Dying in the Netherlands. *JAMA Internal Medicine* **175**, 1633.
Snyder Sulmasy, L. & Mueller, P. S. (2017). Ethics and the Legalization of Physician-Assisted Suicide: An American College of Physicians Position Paper. *Ann Intern Med* **167**, 576-578.
Sofaer, N. & Strech, D. (2012). The need for systematic reviews of reasons. *Bioethics* **26**, 315-28.
Solomon, M. Z. (2005). Realizing bioethics' goals in practice: ten ways "is" can help "ought". *The Hastings Center Report* **35**, 40-7.
Steck, N., Egger, M. & Zwahlen, M. (2016). Assisted and unassisted suicide in men and women: longitudinal study of the Swiss population. *British Jorunal of Psychiatry* **208**, 484-90.
Steinbock, B. (2017). Physician-Assisted Death and Severe, Treatment-Resistant Depression. *The Hastings Center report* **47**, 30-42.
Strand, M., Sjöstrand, M. & Lindblad, A. (2020). A palliative care approach in psychiatry: clinical implications. *BMC Medical Ethics* **21**.

Strech, D. & Sofaer, N. (2012). How to write a systematic review of reasons. *Journal of Medical Ethics* **38**, 121-6.
Sun, Y., Farzan, F., Mulsant, B. H., Rajji, T. K., Fitzgerald, P. B., Barr, M. S., Downar, J., Wong, W., Blumberger, D. M. & Daskalakis, Z. J. (2016). Indicators for Remission of Suicidal Ideation Following Magnetic Seizure Therapy in Patients With Treatment-Resistant Depression. *JAMA Psychiatry* **73**, 337-45.
Swenson, C. R. & Choi-Kain, L. W. (2015). Mentalization and Dialectical Behavior Therapy. *American Journal of Psychotherapy* **69**, 199-217.
Swildens-Rozendaal, W. J. C. & van Wersch, P. J. M. (2015). Regionale toetsingscommissie euthanasie. Code of Practice. https://www.euthanasiecommissie.nl/binaries/euthanasiecommissie/documenten/brochures/brochures/code-of-practice/1/code-of-practice-2015/RTE+Code+of+practice_april+2015.pdf Regional Euthanasia Review Committees (The Hague, the Netherlands). (Accessed Dec 2018).
Symons, M., Feeney, G. F. X., Gallagher, M. R., Young, R. M. & Connor, J. P. (2020). Predicting alcohol dependence treatment outcomes: a prospective comparative study of clinical psychologists versus 'trained' machine learning models. *Addiction* **115**, 2164-2175.
Tanner, R. (2018). An Ethical- Legal Analysis of Medical Assistance in Dying for Those with Mental Illness. *Alberta Law Review* **56**, 149-175.
TheEconomist (2015). 24 & ready to die. https://www.youtube.com/watch?v=SWWkUzkfJ4M.
Thienpont, L., Verhofstadt, M., Van Loon, T., Distelmans, W., Audenaert, K. & De Deyn, P. P. (2015). Euthanasia requests, procedures and outcomes for 100 Belgian patients suffering from psychiatric disorders: a retrospective, descriptive study. *British Medical Journal Open* **5**, e007454-2014-007454.
Thomasma, D. C., Kimbrough Kushner, T., Kimsma, G. L. & Ciesielski-Carlucci, C. (1998). *Asking to Die: Inside the Dutch Debate about Euthanasia* (Kluwer Academic Publishers).
Trachsel, M., Irwin, S. A., Biller-Andorno, N., Hoff, P. & Riese, F. (2016). Palliative psychiatry for severe and persistent mental illness. *The Lancet Psychiatry* **3**, 200.
Trevino, K., McClintock, S. M., McDonald Fischer, N., Vora, A. & Husain, M. M. (2014). Defining treatment-resistant depression: a comprehensive review of the literature. *Annals of Clinical Psychiatry* **26**, 222-32.
Trimbos (2008). Trimbos Netherlands Institute of Mental Health and Addiction, Multidisciplinaire Richtlijn Persoonlijkheidsstoornissen (*Multidisciplinary Guideline Personality Disorders)*. Utrecht, the Netherlands.
Truyts, J. (2020). Psychiater Lieve Thienpont strijdvaardig na vrijspraak op euthanasieproces: "Ik zet mijn werk voort, dat is zeker" https://www.vrt.be/vrtnws/nl/2020/02/02/euthanasieproces-zevende-dag/ (Accessed Feb, 2020).
Turecki, G. & Brent, D. A. (2016). Suicide and suicidal behaviour. *Lancet* **387**, 1227-39.
Turecki, G., Brent, D. A., Gunnell, D., O'Connor, R. C., Oquendo, M. A., Pirkis, J. & Stanley, B. H. (2019). Suicide and suicide risk. *Nature Reviews Disease Primers* **5,** 74.
Tyrer, P., Reed, G. M. & Crawford, M. J. (2015). Classification, assessment, prevalence, and effect of personality disorder. *Lancet* **385**, 717-726.
van de Wier (2019). Drie jaar vechten om te mogen sterven: wachten op euthanasie in de psychiatrie. In *Trouw*. (Published Dec 19 2019)

van Gelder, H. & Bolwerk, P. (2019). Noa's (17) zelfgekozen dood is wereldnieuws geworden, haar familie wil radiostilte. In *Algemeen Dagblad*.
Van, H. L. & Kool, M. (2018). What we do, do not, and need to know about comorbid depression and personality disorders. *Lancet Psychiatry* **5**, 776-778.
Van Orden, K. A., Witte, T. K., Cukrowicz, K. C., Braithwaite, S. R., Selby, E. A. & Joiner, T. E., Jr. (2010). The interpersonal theory of suicide. *Psychological Review* **117**, 575-600.
van Os, J. (2016). New Vision for Psychiatry. *Madness Radio*. https://www.madnessradio.net/new-vision-for-psychiatry-jim-van-os-madness-radio/ (Accessed Jan 2021)
van Os, J., Guloksuz, S., Vijn, T. W., Hafkenscheid, A. & Delespaul, P. (2019). The evidence-based group-level symptom-reduction model as the organizing principle for mental health care: time for change? *World Psychiatry* **18**, 88-96.
Van Thillo, J. & Beel, V. (2020). 'Mensen met autisme kunnen wel degelijk geholpen worden'. In *De Standaard*. (Published Jan 22, 2020).
van Veen, S. M. P., Ruissen, A. M. & Widdershoven, G. A. M. (2020). Irremediable Psychiatric Suffering in the Context of Physician-assisted Death: A Scoping Review of Arguments. *Canadian Jorunal of Psychiatry*. *Revue Canadienne de Psychiatrie.* **65**, 593-603.
van Veen, S. M. P. & van Delden, J. J. M. (2019). Irremediability is key. *American Journal of Bioethics* **19**, 59-60.
van Veen, S. M. P., Weerheim, F. W., Mostert, M. & van Delden, J. J. M. (2019). [Euthanasia of Dutch psychiatric patients in 2015-2017]. *Tijdschrift voor Psychiatrie* **61**, 241-247.
van Waarde, J. A., Scholte, H. S., van Oudheusden, L. J., Verwey, B., Denys, D. & van Wingen, G. A. (2015). A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression. *Molecular Psychiatry* **20**, 609-14.
Van Wel, E. B., Bos, E. H., Appelo, M. T., Berendsen, E. M., Willgeroth, F. C. & Verbraak, M. J. P. M. (2009). De effectiviteit van de vaardigheidstraining emotieregulatiestoornis (vers) in de behandeling van de borderlinepersoonlijkheidsstoornis; een gerandomiseerd onderzoek. *Tijdschrift voor Psychiatrie* **51**, 291-301.
Van Wesemael, Y., Cohen, J., Onwuteaka-Philipsen, B. D., Bilsen, J. & Deliens, L. (2009). Establishing specialized health services for professional consultation in euthanasia: experiences in the Netherlands and Belgium. *BMC Health Services Research* **9**, 220.
Vancayseele, N., Portzky, G., van Heeringen, K., Cloots, H., Hendrickx, E., Kongs, A. & Smets, H. (2018). Agentschap Zorg & Gezondheid. Kenmerken Suicidepogingen in Gent en Vlaanderen. https://www.zorg-en-gezondheid.be/sites/default/files/atoms/files/EZO_su%C3%AFcidepogingen_2017.pdf. (Accessed Feb 2020).
Vandenberghe, J. (2018). Physician-Assisted Suicide and Psychiatric Illness. *New England Jorunal of Medicine* **378**, 885-887.
Vandenberghe, J., Titeca, K., Matthys, F., Van den Broeck, K., Detombe, T., Claes, S., De Fruyt, J., Hermans, M., Lemmens, G., Peeters, D. & Van Buggenhout, R. (2017). Hoe omgaan met een euthanasieverzoek in psychiatrie binnen het huidig wettelijk kader? Adviestekst van de Vlaamse Vereniging voor Psychiatrie (VVP) over te hanteren zorgvuldigheidsvereisten. http://vvponline.be/uploads/docs/bib/euthanasie_finaal_vvp_1_dec.pdf (Accessed Dec 2018).

Vanheule, S., Adriaens, P., Bazan, A., Bracke, P., Devisch, I., Feys, J. L., Froyen, B., Gerard, S., Nieman, D. H., Van Os, J. & Calmeyn, M. (2019). Belgian Superior Health Council advises against the use of the DSM categories. *Lancet Psychiatry* **6**, 726.
Varelius, J. (2016a). Active and Passive Physician-Assisted Dying and the Terminal Disease Requirement. *Bioethics* **30**, 663-671.
Varelius, J. (2016b). On the Moral Acceptability of Physician-Assisted Dying for Non-Autonomous Psychiatric Patients. *Bioethics* **30**, 227-233.
Vergunst, F. K., Fekadu, A., Wooderson, S. C., Tunnard, C. S., Rane, L. J., Markopoulou, K. & Cleare, A. J. (2013). Longitudinal course of symptom severity and fluctuation in patients with treatment-resistant unipolar and bipolar depression. *Psychiatry Research* **207**, 143-149.
Verhofstadt, M., Thienpont, L. & Peters, G. Y. (2017). When unbearable suffering incites psychiatric patients to request euthanasia: qualitative study. *British Journal of Psychiatry* **211**, 238-245.
Verhofstadt, M., Van Assche, K., Sterckx, S., Audenaert, K. & Chambaere, K. (2019). Psychiatric patients requesting euthanasia: Guidelines for sound clinical and ethical decision making. *International Journal of Law and Psychiatry* **64**, 150-161.
Vink, T. (2012). [Reaction on 'assisted suicide in psychiatry; current situation and notes on a recent case']. *Tijdschrift voor Psychiatrie* **54**, 763-5.
Warner, R. (2009). Recovery from schizophrenia and the recovery model. *Current Opinion in Psychiatry* **22**, 374-80.
White, P. D., Rickards, H. & Zeman, A. Z. (2012). Time to end the distinction between mental and neurological illnesses. *British Medical Journal* **344**, e3454.
WHO (2001). World Health Organization; Department of Mental Health and Substance Dependence; Gender Disparities in Mental Health. http://www.who.int/mental_health/media/en/242.pdf.
WHO (2019). WHO: Age-Standardized Suicide Rates: Male: Female Ratio (Per 100,000). Available online: https://www.who.int/gho/mental_health/suicide_rates_male_female/en/ (Accessed August 2019).
Wooderson, S. C., Fekadu, A., Markopoulou, K., Rane, L. J., Poon, L., Juruena, M. F., Strawbridge, R. & Cleare, A. J. (2014). Long-term symptomatic and functional outcome following an intensive inpatient multidisciplinary intervention for treatment-resistant affective disorders. *Journal of Affective Disorders* **166**, 334-342.
Zanarini, M. C. (2009). Psychotherapy of borderline personality disorder. *Acta Psychiatrica Scandinavica* **120**, 373-377.
Zanarini, M. C., Frankenburg, F. R., Reich, D. B. & Fitzmaurice, G. (2012). Attainment and stability of sustained symptomatic remission and recovery among patients with borderline personality disorder and axis II comparison subjects: a 16-year prospective follow-up study. *American Journal of Psychiatry* **169**, 476-83.
Zimmerman, M., Chelminski, I., Young, D., Dalrymple, K. & Martinez, J. (2012). Does the presence of one feature of borderline personality disorder have clinical significance? Implications for dimensional ratings of personality disorders. *Journal of Clinical Psychiatry* **73**, 8-12.
Zuradzki & Nowak (2019). Deep uncertainties in criteria for physician aid-in-dying for psychiatric patients. *American Journal of Bioethics* **19**, 54-56.

Acknowlegdments

This endeavor has been an important learning process, on both an academical and a personal level. It would not have been possible without the input, resources, support, feedback, and inspiration provided by so many persons, whom I have been so fortunate to have in my life. I would like to express my deep gratitude and appreciation to:

My promotor Chris Gastmans, for his skillful guidance since the very beginning of this project, and in fact in the years prior to the start of this PhD. For being such an excellent mentor, who truly listens, never discourages and always supports. I am indebted to him for the learning process this has been and for having been such a wonderful mentor all throughout this endeavor.

My co-promotor Scott Kim, for being so generous with his time and expertise, and, to quote a dear colleague, for never making his mentee feel like a burden. I cannot express my gratitude enough for what I learnt over the past few years thanks to him, and for the know-how he shared, well beyond the boundaries of academic work.

My internal jury members, Bernadette Dierckx de Casterlé, for her invaluable expert input and continued support throughout this process, and Koen Demyttenaere, for his true mentorship ever since my early years as a psychiatry resident.

My external jury members, Sigrid Sterckx and Trudo Lemmens, for their careful review of my dissertation and for their extremely thoughtful feedback, which will be very useful for my future work on this topic. I am truly honored that they both agreed to serve as my external jury.

My colleagues at the Center for Biomedical Ethics and Law, in particular Paul Schotsmans, Kris Dierickx, Herman Nys and Carlos Gómez-Vírseda. I am grateful to Pascal Borry for chairing my public doctoral defense and for his support ever since we met. Special thanks to Mahsa Shabani and Tijs Vandemeulebroucke for their guidance and friendship at crucial points of this process.

My colleagues and mentors at the Department of Bioethics, National Institutes of Health Clinical Center, to whom I will remain indebted. I am extremely grateful to Christine Grady for her leadership and support, as well as to Marion Danis, Holly Taylor, Dave Wendler, Steve Pearson, David DeGrazia, David Wasserman, Ben Berkman, Sarah Hull, Saskia Hendriks, Annette Rid and Joe Millum, for truly broadening my horizons. I am also very grateful to Renee Goodman and Mertis Stallings for their support and assistance throughout my time at the NIH.

My fellow colleagues at the NIH, who have always been so welcoming and from whom I have learnt so much: Jake Earl, Robert Steel, Bernardo Aguilera, Dominic Mangino, Will Shupmann, Camilla Strassle, Ben Schwan, Skye Miner, Sarah Raskoff, Kevin Mintz, Sungwoo Um, Talia Bernard, Madison Churchill, Emma Jardas and all my other colleagues. Special thanks also to Matthé Scholten and Andrew Peterson.

My colleagues and mentors at Georgetown University, in particular Maggie Little, Kevin Donovan, John Keown, Daniel Sulmasy, David Miller, Marti Patchell, Patricia Martin and Martina

Darragh. My time at Georgetown has been both formative and wonderful. Special thanks to Laura Bishop, who has been a true mentor and friend from my very first days in the US, I cannot express enough how important she has been and continues to be.

My colleagues and mentors in the East Coast and beyond, who have been so generous and whom I have been so fortunate to meet: John Peteet, Rebecca Brendel, Sonu Gaind, Tadeusz Zawidzki, Silvia Cannetto, Jerome Wakefield and Jonathan Moreno.

My colleagues and mentors in Belgium, in particular Ludi Van Bouwel and Jan de Lepeleire, who have been so extremely supportive ever since the beginning of this endeavor, as well as Hilde Smets, Rachid Baitar, Hilde Libbrecht, Gert Wouters, Saskia Verbesselt, and my dear colleagues from psychiatry residency training.

My dear friends in the US, from whom I have learnt so much, as scholars and as persons: Diane O'Leary, Marta Barcelos, Mariel Kalkach, Roberta Rassetti, Lucia Galvagni, Maria Kolesarova, Kelso Cratsley and Claire Junga Kim. I am indebted to Georgetown University for the opportunity to have met each of you. Angela Hvitved and Ginger Hoffman, who have been sources of expertise and inspiration on so many levels. Aditi Madan and Courtney Dobrott, for their invaluable friendship since my very first days in the US. Thanks also to Gabriel Colls, Atul Gopal, Gowri Somasekhar and all the wonderful friends I met in the US and who have made this journey so meaningful.

My dear friends from Europe, who have been a continued source of support and motivation: Anna Sierawska, Heleen Lauwers, Julie Callens, Lauren Rasking, Pasquale Cancellara, Eline De Maeght, Ljupcho Efremov, Francesca Maggiani, Gabriella Liuzzi, Irene Caprara, Mela del Carmen Romero Pita, Louiza Kalokairinou, Sherihane Bensemmane, Tim Moons, Pieter De Geyter, Evelien Van Assche, Rahela Habibi, Maira Rodrigues, Curtis Bozek, Xochitl Lopez, Zita Kelemen, Marjorie Trivick, Fulya Dogruel and all my other dear friends.

My brothers Alain and Paul Nicolini, whom I am so grateful to have in my life. My cousin Marta De Ioanna, my aunts Elisabeth Seytre, Gabriella Nicolini and Amelia Nicolini, and all my other dear family members who have been so warm, supportive and appreciative for as long as I can remember.

My parents Dominique Seytre and Fabrizio Nicolini: I cannot express my gratitude enough for their unconditional support and encouragement, love and advice, for never doubting of my abilities and for always urging me to push my boundaries.

My husband Susheel Kumar, for being such a supportive, kind, patient, generous, even-tempered and ever-resourceful partner, thanks to whom I have dared to take leaps of faith in the past, and, hopefully, in the future.

Marie Elisabeth Nicolini

Chevy Chase, Maryland, USA

May 13, 2021