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EUTHANASIA AND ASSISTED SUICIDE IN PSYCHIATRIC PATIENTS: A SYSTEMATIC REVIEW OF THE LITERATURE

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Abstract

The number of psychiatric patients requesting Euthanasia or Assisted Suicide (EAS) continues to increase. The aims of this systematic review were to: 1) describe the available data related to psychiatric patients having received or requesting EAS (pEAS) for each country in which is allowed; 2) and describe the ethically salient points that arise.

PubMed, PsycINFO, and Scopus databases were used to identify articles published up to September 2020. Among the retrieved publications, only studies on pEAS cases (pEAS-C), pEAS requests, or physician reports/attitude towards pEAS reporting some quantitative data on patients having received or requesting pEAS were retained. Among the 24 selected studies, thirteen (54%) were about pEAS in the Netherlands, four (17%) in Belgium, and seven (29%) in Switzerland. Results were different across different countries. In the Netherlands, pEAS-C were mostly women (70-77%) and often had at least two psychiatric disorders (56-97%). Mood disorders were mainly represented (55-70%) together with personality disorders (52-54%). History of suicide attempts was present in 34-52%. Moreover, 37-62% of them had at least one comorbid medical condition. In Belgium pEAS-C were mostly women (75%), but the majority (71%) had a single diagnosis, mood disorder. In Switzerland available data were less detailed.

As pEAS-C seem to be very similar to 'traditional suicides', pEAS procedures should be carefully revised to establish specific criteria of access and guidelines of evaluation of the request. A deeper focus on unbearable suffering, decision capacity and possibilities of improvements is warrented as well as the involvement of mental health professionals.

Highlights

Features of psychiatric patients having received Euthanasia or Assisted Suicide (pEAS) were different across different countries
In the Netherlands the percentage of pEAS cases increased from 0% to 1.1% (from 0 to 68) in 2009-2019
In Belgium the percentage of pEAS cases increased from 0% to 2.2% (from 0 to 40) in 2002-2013
Mood disorders were mainly represented
Cases of pEAS seem to be very similar to ‘traditional suicides’

Introduction

Euthanasia or Assisted Suicide (EAS) (see Box 1 for acronyms mainly used in this manuscript and Box 2 for useful definitions) can be legally practiced in the Netherlands, Belgium, Luxembourg, Switzerland, Colombia, and Canada, as well as in nine states and the district of Columbia within the United States (Emanuel et al., 2016), and Australian state of Victoria. In the Netherlands, Belgium, Luxembourg, and Switzerland, EAS is not restricted to patients at the end of life stage. For instance, in the Benelux countries, "unbearable suffering" due to a medical (somatic or mental) condition that "can not be alleviated" and in the absence of reasonable alternatives is among eligibility requirements for receiving EAS.

The number of patients who request EAS is progressively increasing in countries where this procedure is allowed (Emanuel et al., 2016) and legalising it can have this consequence (Moller, 2020). The same is happening concerning psychiatric patients requesting/receiving EAS. A Duch survey among physicians (n = 1456) found that 2% of all requests were from psychiatric patients (van der Heide et al., 2012). In fact, psychological/mental pain can become intolerable, like or even more than physical pain, and it has overlapping neuroanatomical substrates with physical pain (Eisenberger, 2012). EAS on the grounds of unbearable mental suffering caused by a psychiatric disorder (psychiatric EAS, or pEAS hereafter) remains a limited practice; however, its increasing frequency raises ethical and legal concerns (Lopez-Castroman, 2017; Olie and Courtet, 2016a, b), particularly because of the absence of specific or additional eligibility criteria for psychiatric patients. Indeed, the eligibility requirement of unbearable mental suffering is a condition also commonly experienced by psychiatric patients at suicidal risk (Ducasse et al., 2017).

To date, only a previous review focused on the legal status of EAS and the available data on attitudes and practices was published (Emanuel et al., 2016). To the best of our knowledge, no previous systematic review focused on pEAS.

Aims of the Study

This is the first systematic review with the primary aim to identify and describe the available data related to patients having received or requesting pEAS for each country in which is allowed. We will firstly report results separately for each country since pEAS is regulated by different laws in each one. Our secondary aim, covered in the discussion, is to examine main themes of the included studies and describe the ethically salient points that arise from the empirical literature on this topic. To this aim we reviewed articles concerning all known cases of pEAS (pEAS-C) and pEAS requests (pEAS-R) worldwide.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009). A literature search (articles published until September 30th, 2020) was independently performed by RC and EO using PubMed, PsycINFO, and Scopus databases with the search terms (euthanasia[title] OR "assisted suicid*"[title] OR "assisted dying"[title] OR "physician assistance in dying"[title]) AND (psych*

OR mental) with appropriate filters (abstract, humans, English). We used EndNote software (EndNote X9, Thomson Reuters, USA) to identify the duplicates among the three databases. The reference lists of the identified studies and reviews were also checked to find additional relevant articles.

In Belgium, a previous study analyzed all pEAS cases reported to the Federal Control and Evaluation Committee on Euthanasia (FCEC) (Dierickx et al., 2017). As no analogous study exists for the Netherlands, the summary reports of all EAS cases identified by the Dutch Regional Euthanasia Review Committees (DRERC, Regionale Toetsingscommissies Euthanasie; https://www.euthanasiecommissie.nl), and the End-of-Life Clinic (now Expertisecentrum Euthanasie) annual reports (http://www.levenseindekliniek.nl/informatie/) were analyzed.

Studies were included if: 1) they focused on pEAS-C and/or pEAS-R; 2) they reported some quantitative data on patients having received or requesting pEAS; 3) they were written in English language. All study designs were included. In the case of surveys on physicians' practice towards EAS, only studies considering (also) psychiatric patients were included. Studies were excluded if: 1) they only considered terminally ill patients or patients with a chronic medical condition who could also have a psychiatric comorbidity; 2) they focused on patients with dementia (for reviews on suicide and EAS in dementia see (Diehl-Schmid et al., 2017; Draper, 2015; Tomlinson and Stott, 2015)); 3) they did not report quantitative data but they focused on opinions concerning pEAS; 4) they were case series of extremely small sample size ($n<5$) (e.g., (Benrimoh et al., 2017; Perreault et al., 2019)); 5) they were commentaries, letters to the Editor, reviews (see Figure 1 for the study flowchart). From each included article, RC and DD independently extracted: country of the study, analysed period, sample, male gender, age, ethnicity, medical conditions, psychiatric conditions, main results, and results on psychiatric patients (when different from main results) (Table 1). RC and DD independently evaluated the strength of reporting with the Quality Assessment Tool for Case Series Studies (National Institutes of Health, 2014), the checklist for reporting survey research (Bennett et al., 2010), the COnsolidated criteria for REporting Qualitative research (COREQ) checklist (Tong et al., 2007), and the checklist for reporting observational longitudinal studies (Tooth et al., 2005). In the following description, when studies included overlapping samples of patients, we followed these steps: we mentioned all the studies at the beginning of the related paragraph, we described the more comprehensive study/studies in the text of the results, we included and described each study in the descriptive table (Table 1). In the following text we will use the term "pEAS" when we specifically refer to EAS granted or requested for psychiatric reasons and "EAS" when we refer to EAS in general, not only granted or requested for psychiatric reasons but for every reason.

Results

History and current law

For a description of the history of legislation and current law of states and countries where EAS is allowed see Box 3.

Description of main studies

At the end of the selection process (Figure 1), 24 articles were retained (Table 1): thirteen (54%) were about pEAS in the Netherlands, four (17%) in Belgium, and seven (29%) in Switzerland. Four

main study designs were represented: 1) pEAS case series (n=13; 54%); 2) surveys on physicians' practice of/attitudes towards pEAS (n=6; 25%); 3) qualitative studies (n=4; 17%); and 4) longitudinal study (n=1; 4%). Among the included studies, some described pEAS-C, some pEAS-R, some referred to pEAS request withdrawal, and some described not granted pEAS requests. In the following paragraphs we will present a narrative synthesis of the studies, distinguishing these 4 types when possible.

Netherlands

Prevalence of pEAS

Analysis of the annual reports by the DRERC (from 2002 to 2019) and the End-of-Life Clinic (from 2012 to 2017) indicated that the number of pEAS-C is progressively increasing in the Netherlands, although still limited (Figure 2 and 3). According to DRERC, the percentage of pEAS-C increased from 0% to 1.07% (from 0 to 68) in ten years (2009-2019) (Figure 2), while according to the End-of-Life Clinic the percentage of pEAS-C increased from 6.8% to 8.7% (from 9 to 65) in 4 years (2013-2017) (Figure 3).

Characteristics associated with pEAS

The first studies were performed years before the promulgation of the formal legislation (2002). From a first article concerning the most important reasons for discussing 120 reported cases in the Assembly of Prosecutors General (1991-1995), "primarily mental suffering" was already reported for 6 patients (5%), although no further detailes were specified/were available (van der Wal et al., 1996).

Characteristics of patients were available from: a) the data of the annual reports published by the DRERC (pEAS-C); b) the data of the End-of-Life Clinic (a single study including pEAS-C, pEAS-R, pEAS request withdrawal, and not granted pEAS requests); c) surveys on physicians (both pEAS-C and pEAS-R). We referred to the DRERC data for the description of pEAS-C and to surveys of physicians for pEAS-R because of the limited numbers of pEAS-C reported in the physicians' surveys.

DRERC – pEAS-C

The characteristics of patients who received pEAS were available from the data of the annual reports published by the DRERC and were analysed in some studies, such as (Doernberg et al., 2016; Kim et al., 2016; Miller and Kim, 2017; Nicolini et al., 2019; Tuffrey-Wijne et al., 2018; van Veen et al., 2018).

Three studies in particular analysed pEAS-C: 66 patients who received pEAS in the period 2011-2014 (Kim et al., 2016); 35 new cases who received pEAS in the period 2015-2017 (van Veen et al., 2018); 74 cases who received pEAS for personality and related disorders in the period 2011-2017 (Nicolini et al., 2019) (hence, this sample partially overlaps with the previous ones). The main pEAS-C features of these patients can be summarized as following: they were mostly women (70-77%) and often had at least two psychiatric disorders (56-97%); mood disorders were mainly represented (55-70%) together with personality disorders (52-54%); history of suicide attempts was present in 34-52%; 37-62% of them had at least one comorbid medical condition.

End-of-Life Clinic (Expertisecentrum Euthanasie)

The End-of-Life Clinic is a mobile euthanasia clinic that provides EAS to patients whose requests have been rejected by their physicians, but fulfil the legal criteria for EAS. Analysis of the EAS application forms received by the End-of-Life Clinic during its first year of operation (2012-2013)

(n=645) showed that psychiatric (n=53) or psychological conditions (n=121) were self-reported by 174 applicants (27%) (Snijdewind et al., 2015).

Among these patients with psychiatric/psychological conditions, EAS (and not pEAS for the reason we will explain in the next paragraph) was granted to 8.2% individuals. Moreover, among all the subjects who withdrew their requests, 36.8% had psychiatric/psychological conditions, so the rate of withdrawal was high. Among them, EAS requests were not granted in 43.6% and 15.4% died before decision.

One limitation of this study is that "psychiatric" and "psychological" conditions were inferred from the patients' and families' initial self-reported application form/registration to the End-of-Life Clinic. Such conditions were not further specified or validated by medical records or by a physician's evaluation of the patients. Moreover, psychiatric/psychological conditions were not indicated as the main cause of EAS request but can be comorbid with medical condition(s), so we cannot consider these patients under the label "pEAS". This may be also the reason (or one of the reasons) why numbers reported in Figure 3 are different.

Physicians' surveys

The characteristics of patients who requested pEAS were available through some surveys on physicians' practice of/attitudes towards pEAS, including psychiatrists (Evenblij et al., 2019a; Groenewoud et al., 2004; Groenewoud et al., 1997), general practitioners (GPs) (Jansen-van der Weide et al., 2005), and physicians who certified deaths (Evenblij et al., 2019b).

In the surveys of psychiatrists, not surprisingly the reported numbers of pEAS-R were higher compared to GPs. A first analysis of the data from a survey of Dutch psychiatrists (552 respondents out of 673) indicated that among patients who requested pEAS in the previous two years (n=201, 63% women), the most frequent diagnoses were mood disorder (51%) and personality disorder (64%), or both (48% of patients) (Groenewoud et al., 1997). Among these patients, 64% refused the remaining psychiatric treatment options. In a second study, a further sample of 500 Dutch psychiatrists was considered (Evenblij et al., 2019a). Of the 207 responding psychiatrists, 54% had received at least one pEAS-R and 4% had performed pEAS at least once.

Interestingly, Evenblij et al. investigated patients whose pEAS request was denied (Evenblij et al., 2019a): after the request was not granted, the majority of the patients were still alive (69%); they died by suicide (16%); they died of natural causes (3%); they died as a result of EAS performed by the End-of-Life Clinic (3%); they stopped eating and drinking (1.6%).

Surveys of GPs and physicians who certified deaths give us the picture of the phenomenon from another perspective. In fact, the considered samples did not include only psychiatric patients. Analysis of the results of a questionnaire sent to GPs who were asked to describe the most recent EAS requests they had received (n=1,681 requests) (Jansen-van der Weide et al., 2005) showed that depression (7%) and to be tired of living (17%) were among the reasons for requesting (p)EAS. Moreover, among the 144 patients who withdrew their EAS application, 10% initially requested EAS because of their depression and 22% because they were tired of living. However, in this study depression was listed among the reasons for requesting EAS but it is not clear whether this condition was comorbid and how it has been diagnosed. Hence, also in this case, we cannot consider these patients without doubts under the label "pEAS". Finally, among the 150 patients whose request was refused, 18% were depressed and 37% tired of living.

In a national mortality follow-back study, questionnaires were sent to physicians (n=9,351, response 78%) who certified deaths of patients who died between August and December 2015 (Evenblij et al., 2019b). Out of the 5,361 deceased patients, 183 (3.4%) had a psychiatric disorder; of them,

11.4% requested pEAS and 4.8% received pEAS. The presence of a psychiatric disorder was associated with a lower likelihood of having a EAS request being carried out, even in the case of comorbid severe and life-limiting somatic illness.

Belgium

Prevalence of pEAS

All the pEAS-C reported to the FCEC in the period 2002-2013 were summarized (Dierickx et al., 2017) (for this reason we did not perform an independent review of the FCEC biannual reports, like the one we did for the Dutch DRERC reports, even if an update would be needed). The percentage of pEAS-C increased from 0% to 2.2% (from 0 to 40) in eleven years (2002-2013).

A study examining the first 10 years after legislation (2003-2013) (all euthanasia cases: n=8,752) (Dierickx et al., 2016) reported that the average psychiatric disorders annual change was +0.3%. Physical and psychological suffering increased during years (average annual change: +1.8%), while physical suffering only and psychological suffering only decreased (average annual change: -1.5% and -0.3% respectively). This could correspond to the increase of more complex conditions, including psychiatric disorders and 'tiredness of life', and to the recognition that medical conditions are highly associated with psychological distress.

Characteristics associated with pEAS

FCEC – pEAS-C

The characteristics of patients who received pEAS were available from the data of the Belgium FCEC and were reported in some studies, such as (Dierickx et al., 2016, 2017; Smets et al., 2010).

Among the pEAS-C reported to the FCEC in the period 2002-2013, 117 cases (88 women, 75%) were identified (Dierickx et al., 2017): 71% had only a mood disorder, 10% a mood disorder with another psychiatric disorder, and 19% had other psychiatric disorders. Patients with only mood disorders were generally older than 60 years of age (65%), whereas the others were generally younger than 60. Most patients (74%) reported only psychological suffering while 26% reported both psychological and physical suffering. Interestingly, Dierickx et al. did not include patients with physical diseases.

pEAS-R

An analysis of 100 consecutively referred pEAS-R (Thienpont et al., 2015a) showed that 77 of these patients were women, with an average age at intake of 46±16 years for men and 47±12 years for women. Ninety patients had more than one psychiatric diagnosis, and the most frequent psychiatric diagnoses were depression (n=58) and personality disorder (n=50); however, there was an unusually high number of autism spectrum disorder cases. All 100 were considered competent to request pEAS, and were deemed by the authors to be suffering unbearably and irremediably. At the end of the evaluation, 48 of the pEAS-R were accepted and 35 patients underwent pEAS. Eleven out of these 48 patients decided to postpone or cancel the pEAS. In this last group, eight said that "knowing they had the option to proceed with euthanasia gave them sufficient peace of mind to continue their lives". Thirty-eight people withdrew their requests during the evaluation process. After a follow up period of 1-4 years, 57 of the original 100 patients were still alive, with 9 cases "still in process" and 48 "on hold" because "they were managing with regular, occasional or no therapy". However, this can be also correlated to the high rate of pEAS that were not granted.

Switzerland

Prevalence of pEAS

Switzerland has no central register for EAS-C. The Swiss Federal Statistical Office started to document EAS deaths only since 2011.
In a recent analysis of death records (1985-2014), among 3,666 EAS-C, patients with mental illness only were 61 (2.1%) while patients with mental and somatic disorders were 46 (1.6%) (Bartsch et al., 2019).

Characteristics associated with pEAS

In the study by Bartsch et al., concerning the mentioned 61 patients with mental illness only and the 46 patients with mental and somatic disorders, data on specific psychiatric diagnoses were not reported (Bartsch et al., 2019). However, considering all the 3,666 cases, psychiatric diagnoses – hence with possible psychiatric comorbidities – were present in 13.1% of cases, and in this case specific diagnoses were mentioned, in particular, depression (8.8%), other/not further specified (5.8%), psychosis (0.4%) and bipolar disorder (0.3%).
Several Swiss "Right-to-Die" organizations provide EAS, among them EXIT and Dignitas. Some studies reported EAS-C specifically performed by EXIT (Bosshard et al., 2003; Fischer et al., 2009; Fischer et al., 2008; Frei et al., 2001).
The suicide tourism phenomenon has been also studied. All EAS-C of non-Swiss residents between 2008 and 2012 were reviewed (Gauthier et al., 2015) and compared with those of two previous studies (Bosshard et al., 2003; Fischer et al., 2008). This analysis suggests that the number of pEAS concerning foreigners with mental disorders (including dementia) is increasing: 9 cases (2.7%) in the period 1990-2000 (Bosshard et al., 2003), 12 cases (2.9%) in the period 2001-2004 (Fischer et al., 2008), and 21 cases (3.4%) in the period 2008-2012 (Gauthier et al., 2015).
Interestingly, assisted and unassisted suicides were compared in terms of socio-demographic factors (Steck et al., 2016). While the unassisted suicide rate was higher in men than women, no difference was found for assisted suicides. Higher education was positively associated with assisted suicide and negatively with unassisted suicide; living alone, not having children and absence of religious affiliation were factors associated with both assisted and unassisted suicide (Steck et al., 2016).

Strength of reporting

Assessment of the strength of reporting for the selected studies, according to the study design, indicated that all case series studies had good/fair ratings, with the exception of one with poor reporting because of the partial description of the sample (Bartsch et al., 2019) (Table 2). The question about consecutive cases (investigating if patients received/requested pEAS in the order in which they were identified) was considered not applicable in the majority of the studies because all the published cases/requests that met the criteria might not have been consecutive. We indicated "Yes" only for the two studies explicitedly reporting the term "consecutive" for cases (Frei et al., 2001; Thienpont et al., 2015a). All the surveys on physicians' practice and attitudes did not report evidence of reliability/validity and details on the development of the administered research tool (Table 3).
In most of the qualitative studies (Doernberg et al., 2016; Kim et al., 2016; Miller and Kim, 2017) data collection could not be evaluated because studies were performed using already available data (Table 4). The only longitudinal study is shown in Table 5.
It should be underlined that some of the included studies did not report details concerning psychiatric diagnoses. These are the studies for which the psychiatric diagnosis as a reason for EAS was stated in other terms: primarily mental suffering (van der Wal et al., 1996); psychiatric history (Frei et al., 2001); psychiatric or psychological conditions (Snijdewind et al., 2015). Moreover, for

example, as already underlined, in the study by Jansen-van der Weide et al., depression was listed among the reasons for requesting EAS but it is not clear whether this condition was comorbid and how it has been diagnosed (Jansen-van der Weide et al., 2005). For other studies it was difficult to determine whether the psychiatric disorder was the reason for requesting pEAS or was comorbid to another condition (e.g., (Smets et al., 2010; Snijdewind et al., 2015)).

Discussion

Discussion of main results

Our aims were to: 1) review the scientific literature focused on EAS in psychiatric patients (pEAS) in order to identify and describe for the first time the available data related to pEAS for each country in which the practice is allowed; 2) and describe the ethically salient points that arise from the empirical literature on this topic.

Prevalence of pEAS

As previously reported, (p)EAS is progressively increasing in countries where it is allowed (Emanuel et al., 2016). In the Netherlands, the percentage of pEAS-C increased from 0% to 1.07% in the period 2009-2019 according to DRERC data, and from 6.8% to 8.7% in the period 2013-2017 according to the End-of-Life Clinic. Rates are different because the End-of-Life Clinic provides EAS to patients whose requests have been rejected by their physicians, so total numbers are lower (e.g., 747 total EAS cases at the End-of-Life Clinic in 2017 versus 6,585 at DRERC in the same year).

In Belgium, pEAS-C increased from 0% to 2.2% in the period 2002-2013. In this case total numbers are lower compared to the Netherlands (around 1,800 cases of EAS in 2013) but an update is needed.

Concerning Switzerland it was possible an estimate of the rate of pEAS (2.1%) considering death records of the period 1985-2014 (n=3,666).

Characteristics associated with pEAS

Concerning pEAS-C, both the Netherlands and Belgium patients who received pEAS were mostly women (70-77%). However, in the Netherlands they often had at least two psychiatric disorders (56-97%), while in Belgium the majority (71%) had a single diagnosis. In both countries mood disorders were the main diagnosis (55-71%) while personality disorders were frequent in the Netherlands (52-54%) (and in requestors of pEAS in Belgium) but not in the data from Belgium FCEC database (4%). In the Netherlands a high rate of patients (37-62%) had at least one comorbid medical condition. Interestingly, in the study by Dierickx et al. (Dierickx et al., 2017) (Belgium) patients were selected to be without somatic condition but still 26% of them reported both psychological and physical suffering. However, it should be underscored that data from Belgium derive from a single study, while those from the Netherlands from three studies, making them more likely to be representative. Further, the Belgian paper was based on summary data from the FCEC rather than from more detailed case files as in the Dutch studies.

Concerning pEAS-R, results were similar across different countries, with a majority of women (63-77%), mood disorders (51-58%), personality disorders (50-64%) and medical comorbidity (22-

23%). However, in one case series from Belgium there was a high rate of autism spectrum disorder (Thienpont et al., 2015b).

A comparison can be traced between pEAS-C/pEAS-R and 'traditional' suicide. Women were preponderant in both pEAS-C and pEAS-R (Dierickx et al., 2017; Groenewoud et al., 1997; Kim et al., 2016; Nicolini et al., 2019; Thienpont et al., 2015a; van Veen et al., 2018). This ratio corresponds to the sex ratio among suicide attempters and is the opposite of the sex ratio in suicide deaths (Bachmann, 2018; Canetto and Sakinofsky, 1998; Fox et al., 2017) often attributed to men's use of more fatal means. Thus, the ratio of women to men among pEAS-C is what one would find if a random sample of suicide attempters were given reliably lethal means of suicide. Hence, we can hypothesize that pEAS provides a highly lethal means for women, who are relatively protected against suicide. In fact, in the study comparing assisted and unassisted suicide in Switzerland, the rate of unassisted suicides was higher in men than women while the rate of assisted suicides was similar in both sexes (Steck et al., 2016). This is not the only hypothesis to explain the higher rate of women. Another one is related to different social expectations and norms in relation to traditional masculinity (Moller-Leimkuhler, 2003), that may not be associated with representations related to EAS. Another hypothesis can be related to the preponderance of women having a diagnosis of depression (Hyde and Mezulis, 2020), one of the main diagnoses in pEAS.

Individuals who obtained or requested pEAS are remarkably similar to individuals who die by 'traditional' suicide. In fact psychopathology, particularly mood and personality disorders, and concurrent physical illnesses are among the factors affecting suicide risk (Turecki and Brent, 2016). Moreover, according to Dierickx et al., psychological suffering was the main motivation of EAS-C, in 72% of cases or more (Dierickx et al., 2017). In the same direction we know that higher psychological pain levels are associated with suicidal ideation and attempts (Ducasse et al., 2017). More in general, the analysis of the included studies indicates that – not surprisingly – psychiatric patients who obtained or requested pEAS had frequently a particularly severe symptomatology, with a high rate of psychiatric and physical comorbidities. It is well known that comorbidities are particularly frequent in suicide attempters, especially in re-attempt (Blasco-Fontecilla et al., 2016). Moreover, the role of physical pain in suicidal thoughts and behaviors has been reported (Calati et al., 2016; Calati et al., 2017; Calati et al., 2015). Approximately 1 in 4 patients reported the presence of physical pain, together with psychological pain, despite the absence of reported physical illnesses (Dierickx et al., 2017).

As patients who obtained or requested pEAS seem to have clinical features that overlap with those of unassisted suicides, the current risk could be to convert "traditional" suicides into pEAS or to increase suicide mortality by giving access to lethal methods to suicidal patients. People dying from medical illnesses who receive EAS tend to be empowered people who value self-determination and control. Psychiatric patients in the acute phase of their illness which could lead to suicidal risk may not have these characteristics (American Association of Suicidology, 2017).

Some relevant aspects in mental health

Unbearable and irremediable suffering

In the analysed countries (Netherlands, Belgium, and Switzerland) EAS is not restricted to patients at the end of life stage but is allowed in presence of "unbearable suffering" and in the absence of reasonable alternatives. The concept of unbearable suffering (Dees et al., 2010), and the distinction between unbearable physical suffering and unbearable *mental* suffering are not clear. The presence of intense mental suffering in patients with a psychiatric/psychological condition could limit their

capacity to foresee feasible alternatives and could induce the wish to die. It is a paradox that unbearable psychological suffering is a target for suicide prevention in daily practice and also a required criterion for EAS: in fact unbearable mental suffering may limit the individual capacity of self-determination and control, making it impossible for patients to be eligible for EAS (for data on the moderating effect of decision-making in the relationship between psychological/physical pain and depression see (Alacreu-Crespo et al., 2019)). Furthermore, a patient may experience her/his unbearable suffering as irremediable, but in fact some correlates of suffering, for example economic or resource access issues, could change over time (Verhofstadt et al., 2017). The issue of irremediable/irreversible suffering should be considered also in relation to the high percentage of patients who no longer wish to die and/or withdraw their pEAS request, indicating the possible transient nature of unberable mental suffering and its complexity (Caceda et al., 2017).

Suicidal acts should be considered as the expression of an attempt to escape from psychological suffering. It is possible to find similarities between reasons to request pEAS and taking overdoses of drugs (Bancroft et al., 1976): among 128 subjects interviewed after their recovery from a suicide attempt (overdose), 42% were "escaping from the situation", 52% wanted to obtain "relief from a terrible state of mind", 33% were "seeking help", and 19% were "trying to influence someone". Hence, pEAS may also be a solution to cope with suffering for some patients, while for others pEAS might represent loss of hope, and demoralization.

Someone may argue that, while the perception of unbearable suffering is patient-related, whether the patient's medical condition is incurable and whether or not the suffering can be alleviated should be informed by the involved physician's knowledge and perception-related (Bernat, 2005). However, psychiatrists/clinical psychologists may not always be involved in the pEAS evaluation process.

Medical futility

Irremediable suffering in pEAS is not predictable. Similarly, the prognosis of psychiatric disorders and efficacy of treatment is not predictable. In psychiatry, the issue of medical futility (i.e., uncertain available data on improvements with a specific therapy (Bernat, 2005)) is particularly difficult to determine. Patients' treatment refusal in the context of an uncertain prognosis (e.g., treatment-resistant depression) should be considered in the context of pEAS evaluation. Most of pEAS patients plausibly suffered from a treatment-resistant mood disorder. However, there is still no consensus on the definition of resistance, and it is generally considered only as the absence of a pharmacological response (i.e., a depressive disorder not responding to one antidepressant or two or more antidepressants from different pharmacological classes at adequate dose and duration (Berlim and Turecki, 2007)). A study focused on cognitive behavioural therapy (CBT) in addition to usual care has shown CBT to be an effective treatment for primary care patients with treatment-resistant depression (Wiles et al., 2016).

Psychological understanding

During the pEAS decision process, it is important to identify the forces that can affect decision-making and that could be under-recognized not only by GPs but also by psychiatrists: transference and counter-transference (Hicks, 2006). In some suicidal patients, the request to die can represent a request for a reason to live, for reassurance of their value, or a paradoxical attempt to regain control over their lives. Clinicians' counter-transference reactions could represent an over-identification with the patient and/or, similarly to patients, indicate a low tolerance for situations that are impossible to control (Nicolini et al., 2019). Despite its importance, the assessment of the influence

of transference and counter-transference was not frequent (24% of patients in the article that addressed this issue) (Groenewoud et al., 2004), even if it is highly recommended.

Decision-making

Patients requesting pEAS should have intact decision capacity. Even if psychopathology does not automatically mean the patient lacks mental capacity, it is highly likely to influence his/her decision-making or increase the risk of incapacity. Four criteria for medical decision-making capacity are widely accepted: the ability to understand the relevant information, the ability to appreciate the disorder and the medical consequences of the situation, the ability to reason about treatment choices and the ability to communicate a choice (Appelbaum and Grisso, 1988). Some critics have even suggested that a request for assisted suicide is itself suggestive or even indicative of a lack of decision-making capacity.

Related cognitive impairments raise the question of ability to decide for ending life, and may also alter the stability of such choices. Psychiatric patients seeking pEAS may reverse their decision with time, usually in the direction of initial acceptance to later rejection of pEAS. Inconsistent decisions regarding pEAS are more frequent in depressed patients (Blank et al., 2001).

Patients having a history of suicide attempt have impaired decision-making even after accounting for psychiatric comorbidity (Richard-Devantoy et al., 2014). This susceptibility trait persists beyond the acute depressive state. Consequently, patients requesting pEAS may have limited ability to foresee alternatives and long-term perspectives to select adequate choices. Altered decision making relies on prefrontal dysfunction. Suicidal patients are very often ambivalent about wish to live and wish to die. In fact, after requesting pEAS, some psychiatric patients withdrew their requests or were on hold.

Contrary to what might be expected, physicians do not use, and the review committees do not require, a high threshold of decision-making capacity for requesting(Doernberg et al., 2016; Tuffrey-Wijne et al., 2018). As patients receiving pEAS have conditions known to raise the risk of decisional incapacity, this issue deserves further consideration in policy debates on pEAS (Olie and Courtet, 2016a, b).

The pEAS option as a trigger of change

The high percentage of patients still alive after a not granted pEAS request (69%) and the high rate of pEAS requests withdrawals (37%) can be seen not only as a consequence of the fact that death desire is transient in nature. Another interpretation of these data is that the sole act of requesting (p)EAS (as well as the approval of the request) could trigger a process of change. According to some authors, the EAS evaluation process can be therapeutic and help patients to regain perspective. Thus, some advocate a “two-track approach” during which a recovery-oriented treatment (“recovery track”) should continue in parallel with the pEAS evaluation procedure (“euthanasia track”) (Jones et al., 2017; Vandenberghe, 2018; Verhofstadt et al., 2017).

Some have in the past used paradox in therapy (Bateson, 1972). However, in this light, we may consider the ethical problems related to the proposition of pEAS to patients only for its paradox effect and without considering it as a real option but only a paradoxical one. Furthermore, it should be noted that if an evaluation for pEAS has a therapeutic effect in alleviating suffering, this means that the patient’s suffering is not irremediable.

Strengths and limitations

This is the first systematic review focused on pEAS and the first attempt to describe the available patients' features related to pEAS-C and pEAS-R for each country in which the practice is allowed. As this is a rapidly evolving topic, the related current laws and the available documentation are rapidly changing. However, the amount of information in English in international websites of relevance is limited; the number of studies on this topic is still scant; the studies are extremely heterogeneous, considering both pEAS-C and pEAS-R, with different study designs, and different types of patients. So standard procedures to report the data and open data repositories in English language would be of great help in this field. A major problem is the partial overlap among the studies' samples (e.g., in different studies the same patients were included). Furthermore, some of the included studies did not report details concerning psychiatric diagnoses. Hence, this review is focused on psychiatric patients having received or requesting EAS (pEAS) but we were not able to include only pEAS-C and pEAS-R strictly considered (i.e. only patients for which the unique reason to request EAS is a formally diagnosed psychiatric disorder). Moreover, in general, there is a lack of clarity on how psychiatric diagnoses were obtained, probably with no standardized assessment, especially concerning personality disorder. Finally, there is the issue of comorbidity: in the present review we tried to focus on psychiatric problems as the main reason for EAS request but the rate of cases in which the decision is precipitated by the comorbidity of a psychiatric disorder and a primary somatic problem is much higher and it should be considered in the future.

Conclusion

Given that suicide prevention remains an important public health priority, there is a need to ensure that pEAS is not simply a (highly efficient) way of completing suicide. Currently, there is ample evidence that patients receiving/requesting pEAS are very similar to those who die by suicide. Individual physicians have tremendous leeway in evaluating, performing and reporting cases of pEAS, despite the known difficulties in applying the eligibility criteria. Thus, the current practice may not be optimal to ensure valid and reliable judgments in pEAS evaluations. Some clinicians with experience in pEAS evaluations have argued for a stricter legal framework for pEAS that includes a rigorous futility criterion, but not the patients' refusals of reasonable treatment options; a continued recovery-oriented care in parallel with pEAS evaluation; a sufficiently long and thorough evaluation by multiple assessors; and a prospective multi-expert panel to review pEAS requests, not merely a post-EAS review, with the involvement of mental health professionals; a deeper focus on unbearable suffering, decision capacity and possibilities of improvements. Such a system, combined with close monitoring and research, may be the best way to ensure that highly vulnerable patients' lives are not erroneously terminated. Recently, some new recommendations on pEAS in Flanders were analysed (Verhofstadt et al., 2019b): the need for at least two positive advices from at least two psychiatrists and the two-track approach, focusing simultaneously on the assessment of the patient's EAS request and on that person's continuation of the treatment, were included. However, it should be noted that if there is insufficient evidence base to make highly reliable judgments of irremediability, then adding more opinions into the mix is unlikely to improve the accuracy. Moreover, a specific instrument has been proposed to assess the nature and extent of suffering in psychiatric patients (Verhofstadt et al., 2019a).

For future research, it would be important to: a) systematically determine which are common points and differences between pEAS-C/pEAS-R and suicide victims and suicide attempters; b) compare the increasing numbers of deaths by means of pEAS versus the numbers of deaths by means of suicide in those countries where EAS became legally practiced; c) consider a strict definition of

pEAS (i.e. only patients for which the unique reason to request EAS is a formally diagnosed psychiatric disorder); d) consider cases of comorbidity between a primary somatic problem and psychiatric disorders e) include also studies published in languages other than English (e.g., Dutch) and gray literature.

Fuani Marino

We conclude this paper citing the words of an Italian writer, Fuani Marino, who attempted suicide as a consequence of a severe post partum depression and described her experience in a book some years later (Marino, 2019). In the selected paragraphs the paradoxical nature of pEAS is elegantly described.

"I wonder if it would not be less traumatic for those who want to leave, but also for those who remain, to be able to benefit from an aid. Frankly, I think so. In fact, there is a profound despair, not only in the desire to die, but also in being obliged to find a way to do it. In having to gather your own strengths and alone, with your own hands, kill yourself. This is a moment of extreme fragility and total solitude, because the suicidal aspirant knows that no one will help him and that indeed they will try to divert him from what he thinks - and that in some cases is - the only solution".

"Among these [cases of depressed patients requesting EAS], that of a twenty-four-year-old Belgian girl who, claiming to have always lived, since she was a child, with the deep desire to die, has obtained the opportunity to use euthanasia. I don't think it's a coincidence that once she was given permission, the girl then gave up. The depressed person who has a tendency to suicide experiences the prohibition to die by suicide, and the attempts to avoid it by family members and medical personnel, like a vexation. I think it is similar to what happens to people suffering from anorexia subjected to forced feeding".

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Conflicts of interest

None.

Contributors

Dr. Raffaella Calati performed the search, extracted data from the included studies, assessed their strength of reporting, and wrote the first version of the manuscript. Dr. Emilie Olié and Prof. Philippe Courtet proposed the topic. Dr. Olié contributed to the search of the studies. Dr. Déborah Dassa independently extracted data from the included studies and assessed their strength of

reporting. Dr. Olié, Prof. Gramaglia, Prof. Guillaume, and Prof. Courtet supervised the manuscript writing.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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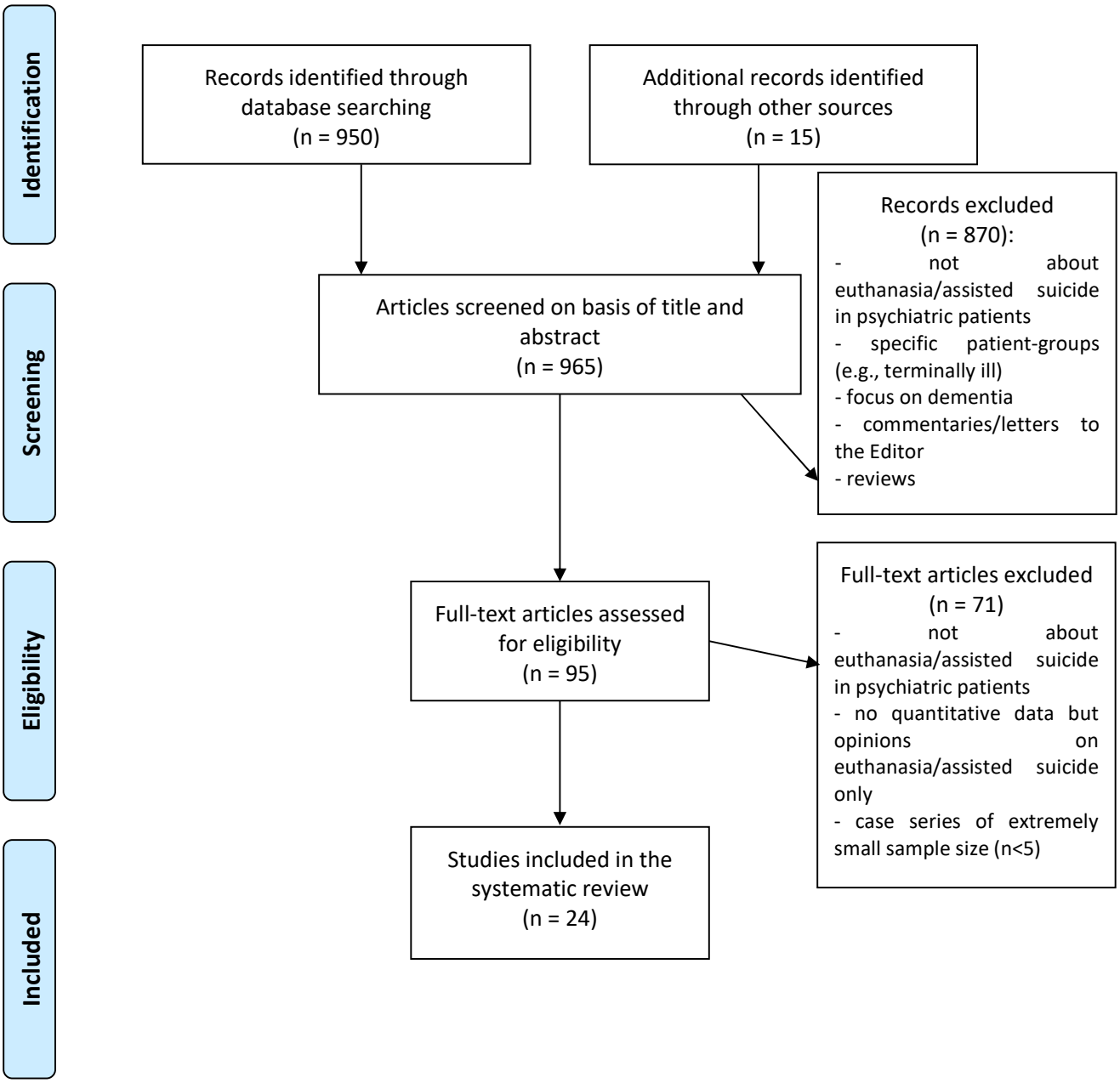
Figures

Figure 1. PRISMA flow diagram.

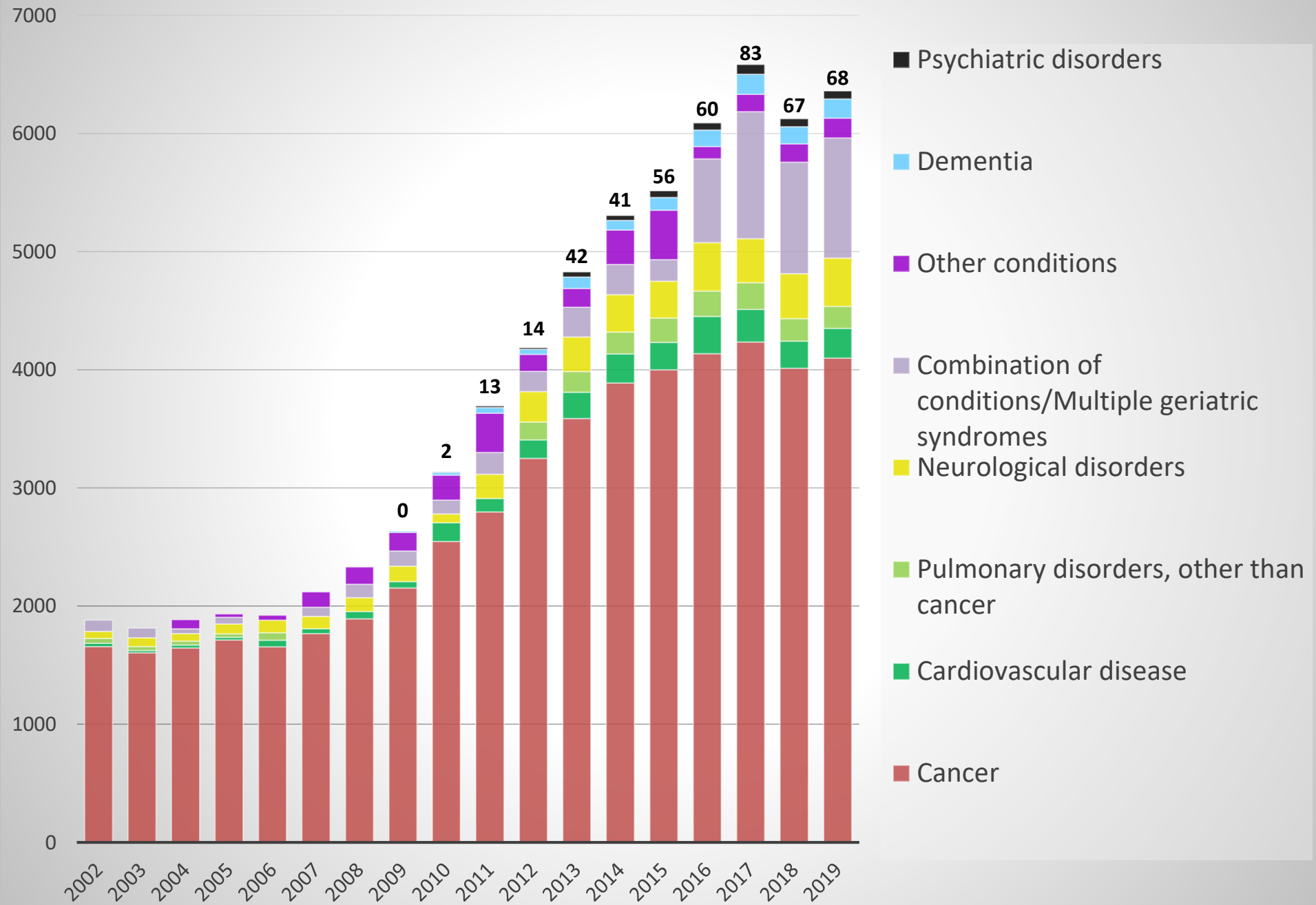
Figure 2. Euthanasia or Assisted Suicide (EAS) summaries identified by the Dutch Regional Euthanasia Review Committees (numbers on bars are numbers of cases with psychiatric disorders). Categories of conditions are the ones reported by DRERC.

Figure 3. Euthanasia or Assisted Suicide (EAS) summaries of the End-of-Life Clinic (numbers on bars are numbers of cases with psychiatric disorders). Categories of conditions are the ones reported by the End-of-Life Clinic.

Figure 1. PRISMA flow diagram.



DRERC EAS summaries



End-of-Life Clinic EAS summaries

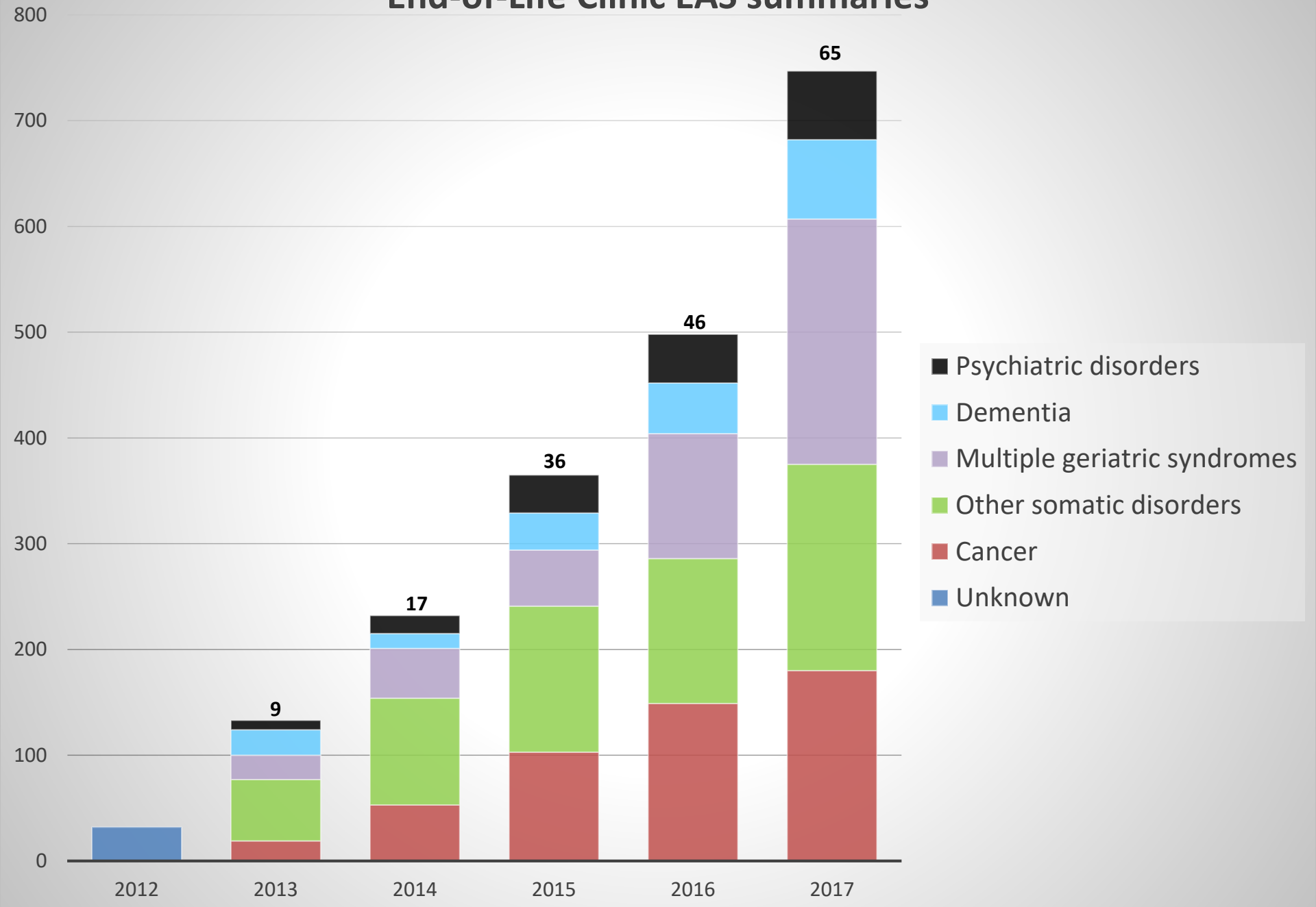


Table 1. Features of the included original studies on euthanasia or assisted dying in psychiatric patients (studies presented for each country are in chronological order).

ADHD: attention-deficit/hyperactivity disorder; COPD: chronic obstructive pulmonary disease; EAS: euthanasia or assisted dying; pEAS: euthanasia or assisted dying in psychiatric patients; GPs: general practitioners; HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder.

Study	Study period	Sample	Sex (men) N, %	Age	Ethnicity N, %	Medical conditions	Psychiatric conditions	Main results	
								General results	Results on psychiatric patients
Netherlands									
(van der Wal et al., 1996)	1991-1995	Interviews: - 405 physicians - 147 physicians who reported EAS cases - 116 coroners - 48 officials Revision of: - 353 judicial files of reported EAS cases - confidential minutes of the Assembly of Prosecutors General (1991-1995) - all published court decisions on EAS cases (1981-1995)	Reported cases: 52% Unreported cases: 62%	Reported cases: 0-49 years: 26% 50-64: 33% 65-79: 27% ≥80: 14% Unreported cases: 0-49 years: 11% 50-64: 17% 65-79: 50% ≥80: 23%	-	Malignant neoplasm Cardiovascular disease Nervous system disease Respiratory system disease Other diseases	Not specified Only "mental suffering" reported	1995: 41% of EAS cases were reported No major differences between reported and unreported cases Of 6324 cases, 13 led to prosecution of the physician	Reason for discussing the reported EAS cases in the Assembly of Prosecutors General: Primarily mental suffering: 6, 5%
(Groenewoud et al., 1997)	1994-1995	Questionnaires sent to Dutch psychiatrists 673 psychiatrists received the questionnaires; 552 responses (83%)	Among the 201 EAS requests for which there were data on the sex of the patient: 74, 36.8% EAS cases: 5, 45%	EAS requests: Mean age: 44.9 (range 16-80) EAS cases: 28-80	-	Among the EAS requests: 45 patients (22%) had also somatic diseases EAS cases: terminal disease (cancer, respiratory, renal and neurologic diseases), or AIDS, severe respiratory disease, or whiplash with post-traumatic epilepsy	Among the pEAS requests: Mood disorder: 103 Psychosis: 29 Other mental disorder (e.g., dissociative and panic disorders): 24 Personality disorder: 46 EAS cases: Mood disorder: 5 Personality disorder: 5 Somatization disorder: 1 Organic mental disorder: 1 Psychosis: 1	In psychiatric practice: The total incidence of pEAS requests was estimated to be about 320 per year pEAS was estimated to occur 2 to 5 times per year	EAS persistent requests: 205 (37%) EAS: 11 Psychiatrist helped the patient to prepare for the suicide in 1 case 1 patient had psychiatric disorders only

									2 patients had no psychiatric disorder
(Groenewoud et al., 2004)	1994-1995	Questionnaires sent to Dutch psychiatrists 673 psychiatrists received the two questionnaires; 552 responses (83%) 221 consultations in view of pEAS	93, 41% of patients seen in consultation	Mean age: 56 (range: 12-92)	-	EAS requests: Physical disorders: 119 EAS cases: Cancer: 21 Neurological disorder: 17 Pulmonary disease: 4 AIDS: 3 Other/multiple: 7 Physical disease, not specified: 8 None: 7	EAS requests: Psychiatric disorders only: 68 Both mental and physical disorders: 19 EAS cases: Mood disorder: 5 Personality disorder: 3 Other/multiple: 3 Not specified: 3 None: 53	Consultants were asked about: Assessment of treatable mental disorders (68%) Patient's decision capacity (66%) pEAS cases: 67, 30% No pEAS: 124, 56%	
(Jansen-van der Weide et al., 2005)	2000-2002	6,596 GPs received the questionnaires 3,614 GPs returned the questionnaires, 60% Patients who explicitly requested EAS: 1,681	54% of patients	<40 years: 3% 40-64: 41% 65-79: 41% ≥80: 15%	-	Cancer: 86% Multiplesclerosis or amyotrophic lateral sclerosis: 2% Old age or general deterioration: 2% COPD: 2% Heart failure: 2% Other: 7%	Not specified Reasons for requesting EAS (among others): Depression: 7%	For all EAS requests: EAS: 44% Patient died before EAS: 13% Patient died before finalization of decision: 13% Patient withdrew the request: 8.6% Physician refused the request: 12%	
(Snijdewind et al., 2015)	March 2012-March 2013	645 EAS requests	Request granted: 57, 35.2% Request rejected: 111, 37.0% Patient died before decision: 48, 38.7% EAS application withdrawn: 30, 50.8%	Request granted: 77±14 Request rejected: 61±22 Patient died before decision: 76±13 EAS application withdrawn: 66±18	-	Cancer Neurologic disease (physical) Neurologic disease (cognitive) Pulmonary Cardiovascular Tired of living Rheumatoid related diseases Other, somatic	Psychiatric or psychological condition	EAS request granted: 162, 25.1% EAS request rejected: 300, 46.5% Patient died before decision: 124, 19.2% EAS request withdrawn: 59, 9.2% Factors independently associated with a granted request: having more than one child and reporting tiredness or loss of autonomy Factors associated with a rejected request: being single, with a psychological condition, and reporting loneliness	Psychiatric or psychological conditions: 174 EAS request granted: 13, 7.5% EAS request rejected: 122, 70.1% Patient died before decision: 18, 10.3% EAS application withdrawn: 21, 12.1%

								or loss of mental capacity	
(Doernberg et al., 2016)	2011-2014	66 cases of pEAS	20, 30%	30-90 years	Reported to be lacking	See (Kim et al., 2016)	Depressive disorder (including psychotic features): 41, 62% Psychotic disorder: 9, 14% Severe eating disorder: 4, 6%	In 36 (55%) cases specific discussion on capacity was limited to general judgments	
(Kim et al., 2016)	2011-2014	66 cases of pEAS	20, 30%	30-90 years	Reported to be lacking	Cancer, suspected malignancy, COPD, cardiac disease, diabetes mellitus, stroke, prior brain tumor surgery, arthritis, orthopedic problems, chronic fatigue, fibromyalgia, migraines, neurological disorder (stroke, Meniere's disease, pain syndrome, Parkinson's disease, diaphragm paralysis, or gait disturbance), pancreatitis, medical complications of severe weight loss, vision loss, hearing loss, incontinence, and decubitus or other ulcers	Depression Anxiety disorder (particularly PTSD) Psychotic disorder Bipolar depression Somatoform disorder Substance abuse Eating disorder Neurocognitive impairment Prolonged grief Autism spectrum Other (including alexithymia, Cotard's syndrome, dissociative disorder, factitious disorder, reactive attachment disorder, kleptomania) Personality disorder or prominent difficulties	The majority of the patients had at least two psychiatric disorders (56%) The most frequent diagnoses were depression (55%) and personality related problems (52%) The majority of patients (58%) had at least one comorbid medical condition	
(Miller and Kim, 2017)	2012-2016	32 cases where the criteria for EAS were not met	14, 43.7%	40–50 years: 2, 6% 50–60: 4, 13% 60–70: 9, 28% 70–80: 5, 16% 80–90: 9, 28% >90: 3, 9%	-	Cancer: 18, 56% Neurodegenerative disease: 6, 19% Many patients had more than one medical condition (stroke, heart failure, tinnitus, vision loss, aphasia and chronic pain) No medical condition: 1, 3.1%	Bipolar depression: 1, 3.1% Another case with: tinnitus, severe hyperacusis and neuralgia together with history of psychiatric disorders (anorexia, PTSD, anxiety and depression)	Procedural criteria not met (improper medication administration or inadequate physician consultation): 22, 69% Substantive criteria not met: 10, 31% (reasonable alternative in 7 cases)	Psychiatric case: both procedural and substantive criteria not met Other case (tinnitus): substantive criteria not met
(Tuffrey-Wijne et al., 2018)	2012-2016	9 euthanasia cases of patients with intellectual disability and/or autism spectrum disorder	3, 33.3%	30-95 years	-	Various conditions	Intellectual disability: 6 Autism spectrum disorder: 3 Additional psychiatric comorbidities (e.g., personality disorder, anxiety disorder, schizophrenia, PTSD)	Both decisional capacity and suffering are difficult to assess in patients with intellectual disabilities	

(Evenblij et al., 2019b)	1st of August and 1st of December 2015	Mortality follow-back study Questionnaires sent to physicians certifying deaths (9,351, 78% responses) 5,361 included in the analyses: 4,243 no EAS request 1,118 EAS request	EAS request: 12.9%	EAS request: Age groups: 17-64: 19.8% 65-79: 14.0% ≥80: 7.8%	EAS request: Non-Western immigrants: 3.1% Dutch, Western immigrants: 11.4%	Causes of death: Cancer: 3,128, 37% Cardiovascular disorder: 540, 15% Pulmonary disorder: 285, 8% Neurological disorder: 518, 12% Other: 890, 27%	Not specified	Of the people with a psychiatric disorder (n=183, 3.4%), 11.4% requested EAS and 4.8% received EAS
(Evenblij et al., 2019a)	May-September 2016	Questionnaires sent to Dutch psychiatrists 500 psychiatrists were selected; 75 did not meet the selection criteria; of the remaining 425 psychiatrists, 207 responded (response 49%)	Of the 9 described cases: 5	Of the 9 described cases: Range 42-82	-	One or more somatic secondary diagnoses: 3	Mood disorder: 5 Personality disorder: 4	Of the 207 responding psychiatrists, 54% had received at least one explicit request for EAS and 4% had performed EAS at least one time Of the 112 responding psychiatrists who ever received a request for EAS, nine answered questions on the most recent case in which they granted an explicit EAS request made by a patient with a psychiatric disorder
(Nicolini et al., 2019)	2011 to October 2017	74 cases of pEAS received for personality and related disorders	18, 24%	18-30 years: 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%	-	62% (n = 46) had one or more physical comorbidities: musculoskeletal and rheumatologic disorders, chronic or generalized pain disorders, neurological disorders, cardiovascular disease and pulmonary disease	38% (n = 28) had only psychiatric diagnoses Depression and bipolar disorder, PTSD or posttraumatic residua, anxiety disorders, somatoform disorders, eating disorders, psychotic disorders, substance abuse, neurocognitive, other, including autism, complicated bereavement, dissociative disorder, alexithymia	All but two patients had comorbid Axis I psychiatric conditions The most common conditions were: depression (unipolar or bipolar), PTSD or prominent post-traumatic symptoms, anxiety disorders, somatoform disorders, and eating disorders
(van Veen et al., 2018)	2015-2017	35 cases labeled as psychiatric were analyzed	23%	>50: 74% 50-70: 51%	-	Somatic comorbidity: 13, 37% Including: cardiac arrhythmias; Alzheimer's dementia; heart failure; COPD; arthrosis; hearing impairment; dizziness; Ehlers-Danlos syndrome; obesity; skin problems; migraine; chronic pain; tinnitus; diverticulitis; spastic quadriplegia; osteoporosis; anemia; and renal dysfunction	Mood disorders: 23, 65.7% Anxiety disorders: 10, 28.6% PTSD: 8, 22.9% OCD: 4, 11.4% Psychotic disorders: 6, 17.1% Somatoform disorders: 5, 14.3% Autism spectrum disorders: 1, 2.9% Substance use disorders: 3, 8.6% Eating disorders: 7, 20.0%	Patients were most often diagnosed with mood disorders (66%) and personality disorders (54%) In 31 cases (89%), at least one independent psychiatrist was consulted for a second opinion, and in all cases an independent specialized euthanasia consultant was involved In all cases, the consulted physicians agreed that the patient was competent to choose for EAS

							Personality disorders: 19, 54.3%	
Belgium								
(Smets et al., 2010)	September 22, 2002-December 31, 2007	1,917 EAS cases	52.7%	<39 years: 3.0% 40-59: 26.0% 60-79: 53.1% >79: 17.9%	-	Cancer: 82.5% Other than cancer: 17.5% Progressive neuromuscular disease Cardiovascular disease Non-malignant pulmonary disease Non-progressive neuromuscular disease AIDS Other	Psychiatric disorders:18 Depression: 5 Psychosis: 1 Huntington's disease: 5 Alzheimer's disease: 5 Creutzfeldt-Jakob disease: 1 Vascular dementia: 1	Compared with natural deaths in the general population, patients who died by EAS were: Younger More often men With cancer With unbearable physical suffering: 95.6% With unbearable psychological suffering: 68% Non-terminal patients: 6.6%
(Thienpont et al., 2015)	October 2007-December 2011; follow-up at the end of December 2012	100 consecutive psychiatric patients requesting euthanasia	23, 23%	47±13 (range 21-80)	-	Not considered in the study	90 patients had >1 disorder Treatment-resistant mood disorder (n=58; n=48 major depressive disorder and n=10 bipolar disorder) Personality disorder (n=50) Both (n=29) PTSD (n=13) Schizophrenia and other psychotic disorders (n=14) Anxiety disorders (n=11) Eating disorders (n=10) Substance use disorders (n=10) Somatoform disorders (n=9) Pervasive developmental disorders (n=8; n= 7 with Asperger syndrome and n=1 with ADHD) OCD (n=7) Dissociative disorders (n=7) Complicated grief (n=6) After the initial evaluation, Asperger syndrome was diagnosed in 12 patients	In total, 48 euthanasia requests were accepted and 35 were carried out Among the other 13 patients: 2 committed suicide before EAS 11 patients decided to postpone or cancel the procedure December 2012: in total, 43 patients had died: 35 by euthanasia 6 by suicide 1 by palliative sedation 1 because of anorexia nervosa Among the 52 patients whose request was rejected: 38 withdrew their requests before decision 8 continued to pursue their requests 4 died by suicide 2 natural deaths
(Dierickx et al., 2016)	January 1, 2003-December 31, 2013	8,752 reported euthanasia cases	2003: 49.4% 2013: 52.0%	2003: 18-59 years: 34.5% 60-79: 48.5% ≥80: 17.0% 2013:	-	2003: Cancer: 84.3% Other than cancer: 15.7% 2013: Cancer: 68.7% Other than cancer: 31.3%	2005: Psychiatric disorders: 0.8% 2013: Psychiatric disorders: 3.9%	The number of reported euthanasia cases increased every year EAS rate increased among people: - aged 80 years or older - who died in a nursing home - with a disease other than cancer

				18-59: 16.5% 60-79: 48.5% ≥80: 35.0%				- not expected to die in the near future
(Dierickx et al., 2017)	September 23 2002-December 31 2013	179 cases of pEAS	Mood disorders: 19, 22.9% Other psychiatric disorders: 7, 31.8% Mood disorders with another psychiatric disorder: 3, 25.0% Dementia: 26, 41.9%	18-59 years: Mood disorders: 29, 34.9% Other psychiatric disorders: 19, 86.4% Mood disorders accompanied by another psychiatric disorder: 10, 83.3% Dementia: 4, 6.5% 80 years or older: Mood disorders: 32, 38.6% Other psychiatric disorders: 1, 4.5% Mood disorders accompanied by another psychiatric disorder: 0, 0.0% Dementia: 25, 40.3%	-	Cases with a combination of psychiatric and physical disorders were excluded	Mood disorders: 46.4% Other psychiatric disorders: 12.3% Mood disorder with another psychiatric disorder: 6.7% Dementia: 34.6%	pEAS cases: 0.25% of all cases in 2002–2007 2.22% of all cases reported in 2013
Switzerland								
(Frei et al., 2001)	1992-1997	43 EXIT suicides were compared with the available data on 425 non-assisted suicides	Among patients with psychiatric diagnosis: 3, 50%	Among patients with psychiatric diagnosis: Age range: 35-87 years	-	Among patients with psychiatric diagnosis: 66.7% (n=4) had a serious physical illness	Mood disorder Psychosis	Patients with psychiatric history: 6, 13.9%
(Bosshard et al., 2003)	1990-2000	748 cases of assisted dying (Swiss residents)	341, 45.6%	Mean age: 72 years (range: 18-101)	Language: German 703, 94.0%	Of the 331 who died in the Canton of Zürich: Fatal conditions: 78.9%	Among the 331 assisted dying cases in the Canton of Zürich:	Assisted dying was more frequent in: German-speaking, more urbanized, and protestant cantons

		331 died in the Canton of Zürich			French: 27, 3.6% Italian: 18, 2.4%	Cancer: 47.4% Cardiovascular/respiratory disease: 11.8% Neurological disease: 12.4% HIV/AIDS: 7.3% Non-fatal conditions: 21.1% Musculoskeletal system disease: 6.0% Pain syndrome: 3.9%	Depression/schizophrenia: 9, 2.7%	Over the study period the annual number of cases assisted by EXIT tripled	
(Fischer et al., 2008)	EXIT (E) and Dignitas (D): 2001-2004 E: 1990-2000	E: 147 cases of assisted dying D: 274 cases of assisted dying E: 149 cases of assisted dying	150, 35.6%	≤44 years: 29, 6.9% 45-64: 140, 33.3% 65-84: 185, 43.9% ≥85: 67, 15.9%	Non-resident in Switzerland (Austria, France, Germany, Great Britain, Israel, United States, other countries): E: 5, 3.4% D: 250, 91.2%	Malignancy: 161, 38.2% Cardiovascular/respiratory disease: 49, 11.6% HIV/AIDS: 2, 0.5% Neurological disease: 103, 24.5% Rheumatoid disease/pain syndrome: 39, 9.3% Other: 54, 12.8%	Mental disorder: 12, 2.9%	Compared with E, D provided more assistance to: - non-residents - younger persons - people with fatal diseases In E, since the 1990s, the number of women and elderly with non-fatal diseases has increased	
(Fischer et al., 2009)	2001-2004	165 cases of assisted dying for which reasons were available	56, 33.9%	≤44 years: 8.5% 45-64: 40.6% 65-84: 42.4% ≥85: 8.5%	-	Malignancy: 33.9% Cardiovascular/respiratory disease: 10.3% Neurological disease: 30.3% Rheumatoid disease/pain syndrome: 10.3% Other: 12.7%	Mental disorder: 2.4%	Reasons for EAS request most often reported by physicians and patients: Pain Need for long-term care Neurological symptoms Immobility Dyspnea Reasons most often reported by patients: Control of circumstances over death Loss of dignity weakness Less able to engage in activities that make life enjoyable Insomnia	Reasons reported by psychiatric patients: Pain Social isolation Weariness of treatments Weariness of life

								Loss of concentration	
(Gauthier et al., 2015)	2008-2012	611 cases of assisted dying of non-Swiss residents	254, 41.5%	Median age: 69 years (23-97)	Country of origin: Germany Great Britain France Italy USA Austria Other	Cancer: 227, 37.2% Neurological diseases: 290, 47.4% Cardiovascular diseases: 93, 15.2% Rheumatic diseases: 150, 24.6% HIV: 8, 1.3%	Mental disorder: 14, 2.3%	Increasing proportion of non-terminal neurological disorders and rheumatic diseases among assisted dying tourists	
(Steck et al., 2016)	2003-2008	Assisted dying: 1,301 Unassisted suicide: 5,708	Assisted dying: 561, 43.1% Unassisted suicide: 4,068, 71.3%	Age range: 25-94 years	Nationality: Assisted dying: Swiss: 1220, 93.8% Foreigner: 81, 6.2% Unassisted suicide: Swiss: 5059, 88.6% Foreigner: 649, 11.4%	Cancer (digestive, respiratory, breast, male genital, others), nervous system (motor neuron disease, Parkinson's disease, multiple sclerosis, other), circulatory system, musculoskeletal, other	Assisted dying: Age group 25-64 years: Mental and behavioral disorders: Mood disorders: Men: 3 Women: 8 Others: Men: 2 Women: 1 Age group 65-94 years: Mental and behavioral disorders: Mood disorders: Men: 9 Women: 21 Others: Men: 5 Women: 1	Assisted dying rate was similar in men and women Unassisted suicide rate was higher in men Higher education was positively associated with assisted dying, and negatively associated with unassisted suicide Living alone, having no children and no religious affiliation were associated with higher rates of both assisted dying and unassisted suicide	
(Bartsch et al., 2019)	1985-2014	Retrospective data on 3,666 EAS	1,475, 40.2%	Median: 73 (18-105 years)	Swiss residents: 1979, 54% Persons domiciled outside Switzerland: 1687, 46%	Will lead to death after a short time: 667, 23.3% Long term somatic illness: 2083, 72.9%	Psychosis: 16, 0.4% Depression: 321, 8.8% Bipolar disorder: 12, 0.3% Other/not further specified: 214, 5.8%	The number of candidates for EAS increased during the study period Following the Swiss Federal Court's promulgation of binding requirements (2006), the documentation contained in the death records for the subsequent period (up to 2014) is more detailed, but still not uniform or complete	61 (2.1%) had only mental illness 46 (1.6%) had mental and somatic disorder

Table 2. Quality of reporting of the included case series studies (n=13) according to the Quality Assessment Tool for Case Series Studies (NA: not applicable).

Study	1 Was the study question or objective clearly stated?	2 Was the study population clearly and fully described, including a case definition?	3 Were the cases consecutive?	4 Were the subjects comparable?	5 Was the intervention clearly described?	6 Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	7 Was the length of follow-up adequate?	8 Were the statistical methods well-described?	9 Were the results well-described?	Quality Rating (Good, Fair, or Poor)
(Frei et al., 2001)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
(Bosshard et al., 2003)	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Good
(Fischer et al., 2008)	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Good
(Fischer et al., 2009)	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Good
(Smets et al., 2010)	Yes	Yes	NA	Yes	Yes	Yes	Yes	No	Yes	Fair

(Gauthier et al., 2015)	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good
(Snijdewind et al., 2015)	Yes	No	NA	Yes	Yes	Yes	Yes	Yes	Yes	Fair
(Thienpont et al., 2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair
(Dierickx et al., 2016)	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Good
(Dierickx et al., 2017)	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Good
(Nicolini et al., 2019)	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Good
(van Veen et al., 2018)	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	No (partially)	Fair
(Bartsch, 2019)	Yes	No	NA	Yes	Yes	Yes	Yes	NA	No	Poor (only partial description of characteristics of the subjects)

Table 3. Quality of reporting of the included surveys (n=6) according to the checklist for reporting survey research described by Bennett et al. (✓: item reported) (NA: not applicable).

Study	Background				Methods										Sample selection				Research tool					Results				Response rates				Interpretation and discussion			Ethics and disclosure			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Surveys of physicians' practice																																						
(van der Wal et al., 1996)		✓			✓	✓		✓								✓	✓	✓						✓	✓		✓	✓	✓		✓	✓	✓			✓		✓
(Groenewoud et al., 1997)	✓	✓			✓	✓	✓	✓	✓							✓	✓		✓					✓	✓	✓	✓	✓	✓		✓	✓	✓			✓		✓
(Groenewoud et al., 2004)	✓	✓	✓	✓	✓	✓	✓	✓	✓							✓	✓		✓					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓
(Jansen-van der Weide et al., 2005)	✓	✓	✓	✓	✓	✓	✓	✓	✓							✓	✓		✓					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓
(Evenblij et al., 2019b)	✓	✓	✓	✓	✓	✓		✓								✓	✓	✓	✓					✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	NA	✓	NA	✓
(Evenblij et al., 2019a)	✓	✓	✓	✓	✓	✓		✓								✓	✓	✓	✓					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	✓

Table 4. Quality of reporting of the included qualitative studies (n=4) according to the COnsolidated criteria for REporting Qualitative research (COREQ) Checklist (✓: item reported; NA: not applicable).

Study	Domain 1: Research team and reflexivity								Domain 2: Study design															Domain 3: Analysis and findings								
	Personal Characteristics					Relationship with participants			Theoretical framework	Participant selection				Setting			Data collection							Data analysis					Reporting			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
(Doernberg et al., 2016)	NA	✓		✓		NA	NA		✓	✓	✓	✓	NA	✓	NA	✓	NA	NA	NA	NA	NA	NA	NA	✓	✓	✓	✓	NA	✓	✓	✓	✓
(Kim et al., 2016)	NA	✓	✓	✓	✓	NA	NA		✓	✓	✓	✓	NA	✓	NA	✓	NA	NA	NA	NA	NA	NA	NA	✓	✓	✓	✓	NA	✓	✓	✓	✓
(Miller and Kim, 2017)	NA		✓	✓		NA	NA		✓	✓	✓	✓	NA	✓	NA	✓	NA	NA	NA	NA	NA	NA	NA	✓		✓	✓	NA	✓	✓	✓	✓
(Tuffrey-Wijne et al., 2018)	NA			✓		NA	NA		✓	✓	✓	✓	NA	✓	NA	✓	NA	NA	NA	NA	NA	NA	NA	✓			NA	NA	✓	✓	✓	✓

Table 5. Quality of reporting of the included longitudinal study according to the checklist for reporting observational longitudinal studies dsecribed by Tooth et al. (✓: item reported; NA: not applicable).

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
(Steck et al., 2016)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	NA	NA	✓	✓	✓		✓	NA	NA	NA	✓	✓	✓	✓	NA	✓				✓	✓