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Expanded access to investigational drugs in psychiatry: A systematic review

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ABSTRACT

Some psychiatric patients have exhausted all approved treatment options. Numerous investigational drugs are currently being developed and tested in clinical trials. However, not all patients can participate in clinical trials. Expanded access programs may provide an opportunity for patients who cannot participate in clinical trials to use investigational drugs as a therapeutic option outside of clinical trials. It is unknown to what extent expanded access occurs in psychiatry. We conducted a systematic literature search on PubMed, Embase, and PscyInfo, with additional information from ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform and FDA/EMA approvals, in order to find all expanded access programs ever conducted, globally, in the field of psychiatry. This resulted in a total of fourteen expanded access programs ever conducted in psychiatry. Given the prevalence of psychiatric disorders, the activity in clinical research in psychiatry, the regulatory framework enabling expanded access, and the impact of psychiatric disorders on patients, their families, and society, we had expected a higher utilization of expanded access. We propose that the psychiatric community, with pharmaceutical industry, should consider establishing and optimizing expanded access programs.

1. Introduction

Every day, patients with Serious Mental Illness (SMI), their families, and psychiatrists encounter the limitations of currently approved psychiatric treatments. In the United States (US) alone, SMI affects approximately 14.2 million people (National Institute of Mental Health, 2022). Although there is no consistent definition of SMI (Gonzales et al., 2022), it generally encompasses (forms of) schizophrenia, bipolar disorder, and depression, which can have a significant effect on a person's life. The prevalence of treatment resistance, that is, lack of response to approved psychiatric treatments, ranges from 20 to 60% of patients with SMI (Howes et al., 2022). Sometimes, this results in patients having to rely on long-term inpatient care. Patients with SMI face a severely reduced life expectancy, which can be 10 to 25 years shorter than that of the general population (Plana-Ripoll et al., 2020). Inevitably, when treatment turns out to be insufficient and patients cannot be treated adequately, suffering, frustration, and feelings of powerlessness will ensue for those involved. Despite significant efforts to improve (access to) treatment, disability caused by mental illness remains among the top ten causes of disability worldwide (GBD 2019 Mental Disorders Collaborators, 2022). To answer the unmet medical need of patients, the field of psychiatry needs novel treatment options. Clinical research on new treatment options is being conducted. As of August 15th, 2023, ClinicalTrials.gov lists 7,454 ongoing trials, either 'recruiting' or 'not yet recruiting', for psychiatric disorders. Correll and colleagues have reported comprehensively on current phase II, and phase III trials in psychiatry, which include many investigational drugs that may potentially be beneficial to patients with SMI (Correll et al., 2023). For schizophrenia, for instance, various therapeutic compounds, including KarXT (xanomeline/trospium chloride), Ulotaront, Brilaroxazine, and Pimavanserin have shown promising results in clinical trials (Corell et al., 2023). While participation in clinical trials is associated with risks and burdens to individual patients, the use of investigational drugs can provide a (limited) chance of benefit for patients who cannot be treated using approved treatment regimens. However, not all patients can participate in clinical trials, due to reasons such as the absence of clinical trials in their geographical area, not meeting inclusion criteria, or having comorbidities that render them ineligible (O'Hara et al., 2017). Calls have been made to 'redesign' clinical trials in psychiatry, from a standard Randomized Controlled Trial (RCT) design to more pragmatic trial

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designs, in order to make sure the study population is more representative of the clinical reality, and to improve shared decision-making about investigational treatments by making trials more 'user-centric,' and improving 'choice awareness' to improve access to investigational drugs in line with patient preferences (Grootens and Sommer, 2022). However, a large number of patients with SMI still cannot participate in clinical trials. For schizophrenia, up to 80% of patients seen in clinical practice cannot participate in clinical trials for schizophrenia (Taipale et al., 2022), and for depression it was found to be 86% of patients that cannot participate in clinical trials (Zimmerman et al. 2002;2015). Despite the initiatives listed, it does not seem that access to investigational treatments has improved for all patients in need.

Patients that are not able to participate in clinical trials might be eligible for expanded access to investigational drugs. Expanded access, sometimes also referred to as early access, compassionate use, pre-approval access, named-patient use, special access or temporary authorization for use (Kimberly et al., 2017), allows eligible patients to use investigational drugs outside of clinical trials. While regulations vary between countries, patients should generally meet the following criteria: A) suffering from severe and/or life-threatening disease, B) having exhausted all approved treatment regimens, and C) not qualify for clinical trials (Darrow et al., 2015). Expanded access is used as an *ultimum remedium* in order to provide eligible patients a small chance at health benefit. Expanded access can be granted on a single-patient/named-patient basis or on a cohort/group basis. Cohort/group-based programs are usually set up by pharmaceutical companies alongside or after completion of late phase II or III clinical trials to allow trial participants, and/or other patients, to try or continue the investigational drug until it is approved for marketing, or when a drug is approved in one jurisdiction but not in another. As the safety and efficacy of unapproved drugs have not definitively been proven, their use is associated with safety risks and uncertainty. Expanded access programs are used to collect so-called 'real-world data', information about the safety, and the efficacy of the investigational treatment, outside of clinical trial settings (Polak et al., 2020). At the same time, expanded access is hindered by practical issues, such as the burdens associated with the application process, restrictive hospital policies, and lack of support by pharmaceutical companies, and funding and reimbursement arrangements (Vermeulen et al, 2021; Gravelin et al., 2022).

Expanded access seems more prevalent in areas outside of psychiatry, predominantly in oncology (Jarow et al., 2016; Polak et al., 2022;2023). The majority of publications in PubMed on expanded access, 53%, consider the field of oncology (Polak et al., 2022). An online survey conducted among oncologists from Europe, North America, South-East Asia, China, Japan, and Australia suggests that the majority of oncologists (75%) are familiar with expanded access (Krendyukov et al., 2022). As far as we know, similar studies have not been conducted among psychiatrists.

To our knowledge, there has been no review of the global use of expanded access to investigational drugs in psychiatry. This paper has a twofold aim. First, it aims to describe the use of expanded access to investigational drugs in the field of psychiatry, and to determine whether expanded access indeed is used *less frequently* in psychiatry than in other fields. Second, it explores possible reasons behind the low uptake of expanded access in psychiatry, and investigates whether these reasons can be ethically justified.

2. Methods

We performed a systematic review in which the databases PubMed, Embase, and PsycInfo were searched on 19 November 2022 to identify all completed or ongoing expanded access programs in the field of psychiatry, globally, using search terms for various synonyms of 'expanded access', and 'psychiatry' (see supplementary file S1). Records were excluded if they did not (also) concern psychiatric disorders (therefore excluding Alzheimer's disease in further analysis) or did not concern expanded access as described in the introduction of this article. We did not limit for other factors, such as study type or publication date.

Records were deduplicated using Zotero, and Rayyan (Ouzzani et al., 2016), and screened individually using Rayyan by SFV, on the basis of article and/or program titles, and, if not conclusive, abstracts, program information and/or full-text articles.

Additionally, ClinicalTrials.gov was searched for 'Psychiatric Disorder', and we applied the 'Expanded Access' filter to find expanded access programs not described in literature. In a later phase of the process, on 20 September 2023, we searched the WHO International Clinical Trials Registry platform with a broader search 'Expanded access', and a search 'Compassionate use' in order to minimize the risk of not finding all expanded access programs available. These programs were also screened individually by SFV based on program titles, and program information. TBP reconciled this search strategy with the results from their recent literature review on expanded access publications (Polak et al., 2023), and their publicly available code (Polak et al., 2020;2022;2023) was used to reproduce their systematic review of expanded access programs submitted in Food and Drug Administration (FDA)/European Medicines Agency (EMA)/National Institute for Health and Care Excellence (NICE) regulatory approvals and reimbursement dossiers to identify possible additional records. Additional records were screened individually by TBP based on program titles and/or program descriptions.

We labelled the records for disease, clinical trial phase, program sponsors, approval status, starting year, program status, location, and patient numbers.

This study adheres to PRISMA guidelines (Page et al., 2021), where applicable for a systematic literature review. The study was not registered beforehand as the aim of our systematic literature review was only to provide an overview of expanded access in psychiatry.

3. Results

The search revealed a total of 661 results; 371 in Embase, 274 in PubMed, and 16 in PsycInfo (see illustration 1). Removing of duplicates resulted in 401 individual records. After screening, 395 records were excluded because they did not concern expanded access to investigational drugs (n=287) or did not concern psychiatric disorders (n=108). A full list of excluded articles and reason for exclusion is available as supplementary table T1. This left six records for further analysis. In total, 18 results were found on ClinicalTrials.gov, of which five programs concerned expanded access to psychiatric treatments; three of which were not yet identified earlier. Additionally, five results were found on the WHO International Clinical Trials registry platform, three of which were not identified earlier. Reproduction of the search strategy used in the review of regulatory approvals (Polak et al., 2020;2022;2023) resulted in two additional records. This resulted in a total of 14 unique expanded access programs.

The fourteen expanded access programs found concern a variety of psychiatric diseases: schizophrenia, major depressive disorder, postpartum depression, treatment-resistant (bipolar) depression, treatment-resistant post-traumatic stress disorder (PTSD), generalized anxiety disorder, narcolepsy, opioid dependence, and autism spectrum disorder (see Table 1).

In seven out of fourteen programs, expanded access is used for (subtypes of) depression, with programs for reboxetine, duloxetine, brexanolone (zulresso), esketamine nasal spray, ketamine subcutaneous injections, esmethadone and D-cycloserine/lurasidone (NRX-101) (WHO, 1999;2006;2018;2020b;2023a;2023b; ClinicalTrials.gov, 1999;2003;2019a;2019b;2023a;2023b; Kennedy et al., 2002; Bayes et al., 2021; Fuertes-Saiz et al., 2021; Samalin et al. 2022). In two out of fourteen programs, expanded access is used for autism spectrum disorders. One of these programs is a vancomycin/fecal microbiota transplant program, that currently enrolls one patient (ClinicalTrials.gov, 2021). The other program concerns cannabidiol (CBD)-enriched cannabis

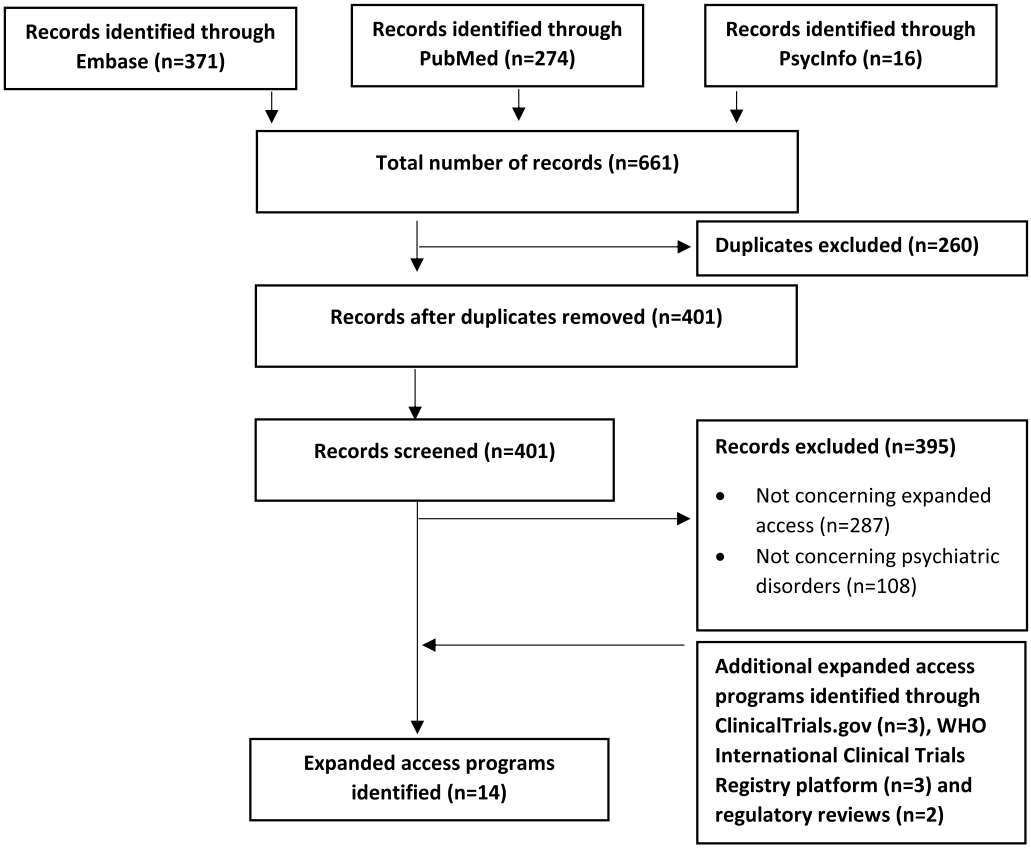

Illustration 1. Flowchart search

extract for 18 patients (Fleury-Teixeira et al., 2019). Two programs concern treatments for opioid dependence; buphrenorphine/naloxone and buphrenorphine extended release (sublocade) (WHO, 1999; Center for drug evaluation and research, 2017). Other indications, as listed above, only have one program ever conducted.

This includes schizophrenia, that has its first (and, to date, last) expanded access program in 1998 (Lançon et al., 2008). This program, concerning sertindole, describes an expanded access program that was set up after the drug was (temporarily) removed from the market. The program supplied the drug to patients who wished to continue using the drug (Lançon et al., 2008). The same method applied for two other programs, that for buphrenorphine/naloxone and buphrenorphine extended release (sublocade) (WHO 1999; Center for drug evaluation and research, 2017).

We have found that expanded access programs in psychiatry are not limited to solely pharmacological treatment, as in one program, MDMA is combined with psychotherapy (WHO, 2020a; ClinicalTrials.gov, 2020; Schmid et al. 2021); a psychiatry-specific application of expanded access.

4. Discussion

In the current study we found a total of fourteen expanded access programs ever conducted in the field of psychiatry, globally, with only four expanded access programs currently running. This confirms earlier data that there are not many expanded access programs in psychiatry (Jarow et al., 2016). This is a small number, as there are over 7,000 clinical trials currently being conducted in the field of psychiatry. Some of these may be beneficial to patients with SMI (Correll et al., 2023).

An example is MDMA-assisted psychotherapy (WHO, 2020a; ClinicalTrials.gov, 2020). After early-phase trials had shown positive results, an expanded access program was set up to provide the treatment for up to 50 patients suffering from treatment-resistant PTSD. Another example is the expanded access program for esketamine nasal spray (SPRAVATO) for treatment-resistant depression. The manufacturer provided the treatment, ahead of marketing authorization, to 66 patients with treatment-resistant depression in France for a duration of six months after phase III clinical trials had shown positive results (Samalin et al., 2022). It was the first time France's expanded access program (called *Autorisation Temporaire d'Utilisation*, or: ATU) was used for a psychiatric treatment (Samalin et al., 2022). Clinical outcomes in the expanded access program were consistent with those in the phase III clinical trials of the drug (Samalin et al., 2022). At the same time, none of the currently ongoing clinical trials of drugs targeting schizophrenia have expanded access programs listed.

By contrast, other fields of medicine have conducted a higher number of expanded access programs, both in absolute numbers (i.e. the total number of expanded access programs), and in relative terms (i.e. the ratio of expanded access programs to the total number of clinical trials). For instance, as of February 26th, 2023, ClinicalTrials.gov indicates that there are 104 currently running expanded access programs for 'Oncology' (out of 29,822 studies; 0,35%), 39 programs for 'Neurologic disorder' (out of 13,760 studies; 0.28%), and 26 programs for 'Cardiovascular diseases' (out of 12,679 studies; 0.21%). While ClinicalTrials.gov may not give an exhaustive overview of all expanded access programs (Borysowski and Górski, 2021), and information is supplied voluntarily by clinical trials sponsors, it seems clear that with only four available programs in psychiatry for 7,454 clinical trials; 0.05%, we may conclude that the use of expanded access is the field of psychiatry is low, and, further, that this lack of expanded access programs is not attributable to a lack of clinical research in psychiatry.

Table 1
Expanded access programs in psychiatry.

Agent	Indication in clinical trial	Location	Sponsor	Clinical trial*	Program status**	Starting year	Number of patients	References
Sertindole	Schizophrenia	Europe	Health authorities in different countries	Post-suspension	No longer available	1998	1,423	(Lançon et al., 2008)
Buprenorphine/ Naloxone	Opioid dependence	United States	National Institute on Drug Abuse (NIDA)	Phase IV	Drug approved for marketing	1999	582	(ClinicalTrials.gov, 1999; WHO, 1999)
Reboxetine	Treatment-resistant depression	Canada	Unknown***	Post-marketing elsewhere	Drug approved for marketing	Unknown***	45	(Kennedy et al., 2002)
Duloxetine	Major depressive disorder Generalized anxiety disorder	Australia	Eli Lilly and Company	Unknown***	Drug approved for marketing	2003	Unknown***	(ClinicalTrials.gov, 2003; WHO, 2006)
CBD-enriched Cannabis sativa Extract	Autism spectrum disorder	Brazil	CBDRx	Unknown***	Program no longer available	2016	18	(Fleury-Teixeira et al., 2019)
Buprenorphine extended release (sublocade)	Opioid dependence	Unknown***	Indivior	Phase III	Drug approved for marketing	Unknown***	Unknown***	(Center for drug evaluation and research, 2017)
Zulresso (brexanolone) injection	Postpartum depression	Unknown***	Sage Therapeutics	Unknown***	Drug approved for marketing	2019	Unknown***	(WHO, 2018; ClinicalTrials.gov, 2019a)
Esketamine Nasal Spray (SPRAVATO)	Treatment-resistant depression	Mexico, Europe***	Janssen	Post-marketing elsewhere	Drug approved for marketing	2019	66 in France, 7 in Spain, unknown in other countries	(ClinicalTrials.gov, 2019b; Fuertes-Saiz et al., 2021; Samalin et al., 2022; WHO, 2020b)
Ketamine subcutaneous injection	Treatment-resistant depression	Australia and New Zealand	Unknown***	Unknown***	Unknown***	Unknown***	Unknown***	(Bayes et al., 2021)
MDMA-assisted psychotherapy	Treatment-resistant post-traumatic stress disorder	United States, Switzerland	Multidisciplinary association for psychedelic studies	Unknown***	Expanded access available	2020	Up to 50 patients	(WHO, 2020a; ClinicalTrials.gov, 2020; Schmid et al, 2021)
Vancomycin and fecal microbiota transplant	Autism Spectrum Disorder	United States	ProgenaBiome	Unknown***	Expanded access available	2021	1	(ClinicalTrials.gov, 2021)
D-Cycloserine and lurasidone (NRX-101)	Treatment-resistant bipolar depression	United States	NeuroRx	Phase II	Expanded access available	2023	Unknown**	(WHO, 2023a; ClinicalTrials.gov, 2023a)
Esmethadone (REL-1017)	Major depressive disorder	United States	Relmada Therapeutics	Phase III	Expanded access available	2023	Unknown**	(WHO, 2023b; ClinicalTrials.gov, 2023b)

* : Clinical trial phase in which the expanded access program started
** : Referring to the situation in the United States
*** : (Other) data lacking in scientific literature (as cited), and could not be found publicly
Data correct at the time of the initial search

4.1. Reasons for the low uptake of expanded access

The low uptake of expanded access to investigational drugs in psychiatry can possibly be explained by various reasons. Firstly, there are fewer clinical trials currently ongoing in the field of psychiatry than there are in other medical fields, such as oncology or neurology. Secondly, for many psychiatric disorders, there is a multitude of treatment approaches involving multiple different treatment modalities, including biological interventions, psychotherapeutic approaches, and social support interventions. Considering pharmaceutical treatment alone, the FDA lists 1,396 (forms of) prescription drugs for depression on their FDALabel search engine (https://nctr-crs.fda.gov/fdalabel), as of September 24th, 2023. This might pose challenges for treating psychiatrists when determining whether patients have exhausted approved therapies, and become eligible for expanded access. Thirdly, psychiatrists have been found to be reluctant in prescribing *approved* 'last-line treatments' or 'drugs of last resort' (Howes et al., 2012; Lappin et al., 2022). If physicians are already reluctant to prescribe approved last line treatments or drugs of last resort, they may even be (far) less likely to pursue *unapproved* treatments for their patients. By illustration, clozapine, an approved antipsychotic drug that is widely recognized for its efficacy in patients with treatment-resistant schizophrenia who have failed to respond to two or more antipsychotics, is known for being underutilized as a drug of last resort (Howes et al., 2012). If patients with treatment-resistant disease are not prescribed approved 'last-line treatments', they may not qualify for expanded access to investigational drugs, as one of the eligibility criteria for expanded access is that the entire approved therapeutic spectrum has been exhausted. Fourthly, in the medical community, psychiatric disorders may be perceived (sometimes incorrectly) as less severe, and/or life-threatening than somatic disorders, and there may therefore be less perceived need for expanded access in psychiatry than in other disease areas (Campbell and Williams, 2021). Fifthly, there are fewer expanded access resources available to psychiatrists than for other medical specialists. The FDA, for instance, has set up a program aimed at facilitating the process of expanded access for treating physicians, but it is focused exclusively on oncology (Scepura et al., 2021). Sixthly, practical considerations, such as lack of institutional support, lack of physicians' familiarity with the

process, unwillingness of pharmaceutical companies' to provide drugs free of charge, concerns from insurers, and administrative complexities, might further contribute to the limited uptake in clinical practice. Specifically considering the four expanded programs that are currently available we find that for three of the four programs (MDMA-assisted psychotherapy, NRX-101 and Esmethadone) information about the expanded access program is available on the sponsors' website. This would have been expected under the 21st Century Cures Act, that demands pharmaceutical companies to supply information about their expanded access policies, but that has been criticized in literature for not being implemented fully (Kang et al., 2021). Finally, it is generally assumed (again, sometimes incorrectly) that psychiatric illness will impede patients' decisional capacities, which may threaten the feasibility of an adequate informed consent process that has been discussed in literature as an issue in the application of expanded access in minors (Wehrmann et al., 2020).

In sum, we have seen that expanded access to investigational drugs is not often used in the field of psychiatry. While the possible advantages of expanded access may be slim, and 'magic bullets' for psychiatric diseases have yet to be found, just like in other (somatic) fields of medicine, there are groups of patients in psychiatry that experience severe unmet medical need, and satisfy the criteria for expanded access to investigational drugs. Pharmaceutical companies could consider setting up expanded access programs alongside clinical trials in psychiatry. For individual psychiatrists it might be beneficial to familiarize themselves with the process of expanded access, so that they can adequately inform eligible patients about relevant opportunities to access investigational drugs.

4.2. Limitations

Our study has several limitations. Firstly, our search may not have been exhaustive. Despite using various scholarly resources, regulatory applications, the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov, information regarding existing expanded access programs proved challenging to find. For example, not all expanded access programs were listed on ClinicalTrials.gov, as has been pointed out elsewhere (Borysowski and Górski, 2021). Secondly, our search was made more challenging by inconsistent use of terminology throughout the field. For example, on ClinicalTrials.gov, the term 'compassionate use' was sometimes used to refer 'off-label use'. Therefore, ClinicalTrials.gov indicates a higher number of expanded access programs than we found on closer examination of literature, and application data. Thirdly, some of the information about the programs is quite sparse, lacking data on program status, and the number of patients that could be enrolled or had been enrolled, even for programs that had been ongoing for a considerable amount of time or were already completed. Possibly, pre-registration of expanded access programs might alleviate some of these problems. Lastly, it is challenging to definitively determine if the uptake of expanded access in psychiatry should be considered low, as it is a subjective judgement. In this study, we opted to compare the availability of expanded access programs in psychiatry to the availability in somatic medicine, but alternative choices could have been made.

4.3. Future research

Future research could focus on further exploring the factors contributing to the limited utilization of expanded access in the field of psychiatry, and gaining insights from relevant stakeholders. One area of interest is investigating why expanded access programs are not commonly set up alongside phase III clinical trials. Furthermore, previous research suggests that patients in other medical fields desire to be informed about, and have access to, (information about) investigational drugs (Bunnik and Aarts, 2019), but this has not been explored for patients with SMI. Additionally, it might be worthwhile to examine how shared decision-making in psychiatry can be improved to include these types of non-standard treatments. Moreover, ethical considerations need to be explored. It seems difficult to determine whether physicians are morally obliged to offer expanded access to patients, as, per definition, the treatments are not yet approved, and safety and efficacy information is not always available, yet the process may provide additional, but small, options for patients (Vermeulen et al. 2023). Treating physicians face additional ethical dilemmas when patients may not have the ability to provide informed consent or have limited decision-making capacity due to psychiatric illness. Therefore, it is necessary to investigate the moral implications of impaired decision-making capacity (due to psychiatric illness) for patient access to investigational drugs.

4.4. Conclusion

To conclude, this study is the first to empirically characterize the use of expanded access to investigational drugs in the field of psychiatry. Expanded access is used to treat psychiatric diseases, albeit on a small scale, and seemingly limited to specific types of (non-psychotic) diseases. Most expanded access programs (eight out of the fourteen programs we found) were only set up in recent years. The field of psychiatry could benefit from further examination of the factors that prevent or hinder the current use of expanded access, and from exploring whether, and under what conditions, expanded access programs should more frequently be set up alongside clinical trials of investigational drugs for psychiatric disorders.

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Stefan F. Vermeulen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Tobias B. Polak:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Eline M. Bunnik:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

TBP reports receiving grants from HealthHolland, and Prins Bernhard Cultuurfonds; receiving personal fees from and owning stock/stock options (<0.01%) in myTomorrows, a service provider in expanded access; and being an unpaid member of the New York University Grossmann School of Medicine Ethics and Real-World Evidence Working Group. myTomorrows was not involved in this research and TBP is contractually free to publish all research activities. SFV and EMB declare no competing interests.

Data availability

The authors are open to requests for data collected during the study. Please contact the corresponding author for any inquiries.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115554.

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