



Identifying outcomes for depression that matter to patients, informal caregivers, and health-care professionals: qualitative content analysis of a large international online survey

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Summary

Background Many clinical trials have assessed treatments for depressive disorders and bipolar depression. However, whether, and which, assessed outcome domains really matter to patients, informal caregivers, and health-care professionals remains unclear.

Methods We did an international online survey in French, German, and English. Participants were adult patients with a history of depression, informal caregivers, and health-care professionals, recruited by purposeful sampling. To identify outcome domains, participants answered four open-ended questions about their expectations for depression treatment. We disseminated the survey without restriction via social media, patient and professional associations, and a media campaign. Four researchers independently did qualitative content analyses. We assessed data saturation using mathematical models to ensure the comprehensive identification of outcome domains.

Findings Between April 5, 2018, and Dec 10, 2018, 1912 patients, 464 informal caregivers, and 627 health-care professionals from 52 countries provided 8183 open-ended answers. We identified 80 outcome domains related to symptoms (64 domains), such as mental pain (or psychological or psychic pain, 523 [17%] of 3003 participants) and motivation (384 [13%]), and functioning (16 domains), such as social isolation (541 [18%]). We identified 57 other outcome domains regarding safety of treatment, health care organisation, and social representation, such as stigmatisation (408 [14%]).

Interpretation This study provides a list of outcome domains important to patients, informal caregivers, and health-care professionals. Unfortunately, many of these domains are rarely measured in clinical trials. Results from this study should set the foundation for a core outcome set for depression.

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Introduction

Depression (depressive disorders and bipolar depression) is a frequent disorder, with a lifetime prevalence of about 15%–18% and a mortality rate ratio of 2.07^{1–3}. This disorder is the fifth most common cause of years lived with disability worldwide.⁴ Despite thousands of trials of pharmacological and non-pharmacological interventions for depression, the clinical interpretation of results is still debated, because of two main reasons regarding the outcomes.^{5–9} First, the heterogeneity of outcomes, in terms of domains (what is measured) and measurement instrument (how the outcome is measured), limits the comparison and combination of results.¹⁰ For example, a meta-analysis comparing seven psychotherapeutic interventions for major depressive disorder across 198 studies identified 33 different outcome measurement instruments used in trials.¹¹ Most of these instruments claimed to measure depression, but their content varied considerably.¹² Second, we do not know whether the domains

assessed in trials matter to people with a lived experience of depression (hereafter called patients, even though some might not have sought professional help), informal caregivers, and health-care professionals. Clinical trials of depression have been criticised for measuring domains that do not matter to patients.⁹ For example, sick leave or impaired relationships are not part of the Hamilton Depression Rating Scale (HDRS) or the Montgomery and Asberg Depression Rating Scale (MADRS), both mandatory scales for drug approval by the US Food and Drug Administration (FDA). However, if trialists want to use outcome measures other than these two scales in phase 3 trials to support an indication of major depressive disorder, they need to seek advice from the US FDA before initiating studies.^{13,14}

A core outcome set (COS) is an agreed on set of outcomes that should be measured as a minimum in all trials of a given condition to allow for combining and comparing their results, for instance, in a meta-analysis.

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Research in context

Evidence before this study

Results of depression trials are controversial because the relevance of the outcome domains (what is measured) for clinical practice and for patients is questioned and there is substantial heterogeneity in the measurement instruments used to assess outcomes across studies. Core outcome sets (COSs) are standard sets of outcomes that should be measured as a minimum in clinical trials of a given field, thus facilitating the comparison and combination of trial results. Involving patients, informal caregivers, and health-care professionals in the development of COSs allows for the selection of outcomes that matter to these end users of research. Developing a COS for depression (depressive disorders and bipolar disorder) could address these two above-mentioned issues.

We searched PubMed from inception to March 9, 2020, for articles related to a COS in depression. The search was done with no language restriction and with the following terms in titles and abstracts ("core outcome set" OR "COS" OR "standard set") AND ("depress*"). We identified one paper published by Obbario and colleagues for the International Consortium for Health Outcomes Measurement (ICHOM), involving 22 experts and two patients, which proposed a set of outcomes for quality of care. We also asked the Core Outcome Measures in Effectiveness Trials Initiative (COMET) in November 2017 about the possible ongoing development of a COS for depression. No development of COS was registered for depression.

We did a similar search for articles related to outcomes that matter to patients with the following terms ("important outcome" OR "relevant outcome" OR "patient-reported outcome" OR "patient-important outcome" OR "PROM" OR "need*" OR "expectation*" OR "preference") AND ("depress*"). We found one systematic review of four studies investigating patient preferences regarding medication-associated outcomes in mental disorders. Among the four included studies, only one involved patients (and only eight) in generating outcomes.

We also found two narrative reviews calling for the use of fatigue and quality of life as interesting outcomes in the treatment of depression, but these two papers did not refer to patient perspectives. Finally, we found several calls from opinion leaders, in viewpoints or discussions, to improve patients' perspectives in depression clinical research and especially in the definition of outcomes.

Added value of this study

We identified a comprehensive list of 80 outcome domains related to the benefits of treatments, derived from the lived experience of depression of a large sample of 3003 patients with depressive disorders or bipolar depression, informal caregivers, and health-care practitioners, in 52 countries. Some outcome domains were frequently mentioned by participants but are not measured by the seven most used depression scales (Hamilton Depression Rating Scale, Beck Depression Inventory, Montgomery and Asberg Depression Rating Scale, Inventory of Depressive Symptomatology, Zung-Self-rating Depression Scale, Center of Epidemiologic Studies-Depression scale, Patient Health Questionnaire 9). We identified 57 other outcome domains unrelated to the benefits of treatment, such as domains on treatment safety, health-care organisation, and social representation of depression.

Implications of all the available evidence

All outcome domains identified in this study matter to patients and could be targets for interventions in depression. Our study sets the foundations for the development of a COS for depressive disorders and bipolar depression. This research is also a panorama of the lived experience of depression. Health-care professionals could use it as a framework in their consultations to engage discussions on issues that matter to patients but that might not spontaneously be talked about in consultation. Finally, our study might inform policy makers on the health and social needs of patients with depression and their informal caregivers, to define health indicators based on issues that are important for patients.

Use of a COS in all depression trials could solve the problem of heterogeneity of outcomes.¹⁵ To ensure that the outcomes included in the COS matter to patients, informal caregivers, and health-care professionals, these individuals should be involved in the development of the COS.¹⁵⁻¹⁷ These sets are developed in a three-step approach: generation of an exhaustive list of outcome domains of interest for the given disease or disorder, selection among these outcome domains of a short list that will constitute the COS, and matching the domains of the COS with corresponding measurement instruments.

In this study, we provide results for the first step of the development process of a COS and identify a comprehensive list of outcome domains for depressive disorders and bipolar depression that matter to patients, informal caregivers, and health-care professionals across different countries and languages.¹⁸

Method

Study design

We did an online international survey with open-ended questions aimed at patients, informal caregivers, and health-care professionals. The survey was available in three languages (French, English, and German) on a secure website specifically designed for the project.

Participants and recruitment

Three groups of participants were included: patients reporting a depressive disorder (including bipolar depression), informal caregivers defined as anyone involved in the care of a patient with depression (eg, family members or friends), and health-care professionals working with patients with depression (eg, psychiatrists, psychologists, general practitioners, nurses). Participants had to speak one of the three study languages.

Panel: Open-ended questions asked of participants and tailored to their group (patients, informal caregivers, health-care professionals)

Open-ended questions for patients

- "For you, what is the most difficult aspect of depression to live with or endure?"
- "For you personally, what might improve or refine treatments for depression?"
- "What prompted you to seek out a health-care professional?" (asked if the participant previously reported having a follow-up for depression)
- "What made you consider yourself as no longer depressed?" (asked if the participant reported having overcome depression in the first question of the survey)

Open-ended questions for informal caregivers

- "What do you consider to be the most difficult aspects to live with for your family member/friend with depression?"
- "What do you consider most important to address in a depressed person?"
- "What types of improvement do you expect from the treatment of depression for your family member/friend?"

Open-ended questions for healthcare professionals

- "According to your experience, what do you consider to be the most difficult aspects to live with for your patients with depression?"
- "According to you, what aspects of their condition should be prioritised for depressed patients?"
- "Under which criteria do you consider a patient to be cured of his/her depression?"
- "In the case of rheumatoid arthritis, studies have for a long time used the number of painful and swollen joints to evaluate treatment efficacy. However, it has been shown that patients expect a reduction in their level of fatigue. Ever since, fatigue has been measured in efficacy studies. According to you, which criteria would be essential to measure in treatment efficacy studies for depression?"

For more on the **online survey** see <http://clinicaledemio.fr/depression/en/>

See **Online** for appendix 3

To capture the diversity of perspectives regarding what outcome domains are of value, we used purposeful sampling, targeting websites, and social media dedicated to depression (appendix 3).¹⁹ During recruitment, we assessed monthly the diversity of the population on the following characteristics: age, gender, disease severity (measured by the Patient Health Questionnaire 9 [PHQ-9]), socioeconomic status for patients; gender and type of relationship to the relative with depression for informal caregivers; and profession (psychiatrist, psychologist, general practitioner, nurse) and workplace (hospital and private practice) for health-care professionals. The online recruitment of patients older than 70 years was insufficient, so we recruited ambulatory patients and inpatients, and administered the survey with face-to-face interviews.

All participants provided informed consent online before enrolment. The Institutional Review Board of the National Institute for Medical Research (INSERM) in France gave ethical approval for the study (IRB00003888), as did the Ethic Committee of Oberösterreich in Austria.

Data collection

We asked closed-ended questions to patients, informal caregivers, and health-care professionals to collect sociodemographic and health characteristics. For patients, we collected sociodemographic characteristics, such as age, gender, and education, and health characteristics,

such as the severity of the depression assessed by the PHQ-9, the number of suicide attempts, the number of lifetime depressive episodes, and duration of the last depressive episode. For informal caregivers, we collected data, among others, on their relationship with the person with depression, including whether they were living with the individual, and their own history of depression. For health-care professionals, we collected data, among others, on professional characteristics (eg, profession, experience, workplace), personal history of depression, and history of depression of a relative (appendix 3).

We asked open-ended questions to capture outcome domains that matter to participants. We searched for a translation of the scientific goal of the study (identifying outcome domains) into participant concerns (expected benefit of treatments) during a qualitative pilot study in France, involving face-to-face interviews with six patients, two informal caregivers, and 11 health-care professionals (appendix 3). From this pilot study, we developed, for each of the three groups, three to four open-ended questions for identifying domains (panel). We focused the questions on participants' perspectives of the expected benefits of depression treatment to allow for identifying domains for clinical effectiveness research.

We developed a specific website to host an international online survey with open-ended questions and tested the online survey for usability, clarity, and wording with nine patients, ten health-care professionals, and seven informal caregivers during face-to-face interviews in France. Their feedback helped to improve the survey and website before translation (with a translation and back-translation method) into English and German by native speakers.

Analyses

Analyses were restricted to participants who completed at least one open-ended question. We identified domains with an inductive multiple-round qualitative content analysis in three steps: the open coding of the manifest content of all units of meaning corresponding to expectations for depression treatment in each language, the development of a list of emergent categories in English, and the identification of outcome domains related to the benefits of depression treatment.^{20–23}

During the first step, two researchers read all responses in each language. Then they independently coded the responses—ie, they identified within each response units of meaning (any expression found in the text expressing an expected benefit of depression treatment) and assigned them a code. For example, the text "I could not sleep at night and I felt always tired" was coded as insomnia and fatigue. In case of discrepancies, consensus was reached by discussion. One of the researchers (ACh) coded responses in all languages, and three other researchers (AT, BT, CLB) double-coded responses in their mother tongue. To reduce interpretation bias, coders had different backgrounds and training (psychiatrists, social scientists,

training in cognitive behavioural or psychodynamic therapies). For each language, coders developed a codebook (ie, collection of codes).²¹ To avoid missing domains, we coded any unit of meaning mentioned by participants, even when units of meaning appeared unsuitable as potential domains (eg, shorter wait lists, or less reluctance to seek help). In aiming for high granularity of the encoded information, we kept separate close units of meaning (eg, we considered to be lonely different from to feel lonely).

During the second step, the four coders (ACh, AT, BT, CLB) and a patient (ST) merged and categorised all codes from the French, German, and English codebooks into a unique list of domains, in English, by using semantic considerations, clinical judgment, available clinical literature, and patient expertise. They discussed a balance between sustainable granularity and acceptable loss of information for each category.

During the third step, the investigators classified domains into two categories on the basis of their clinical expertise (ACh, AT, CLB), clinical trial expertise (ACh, AT, BT, VTT, PR), and patient expertise (ST): domains to assess the benefits of depression treatment (eg, improvement of symptoms) and other domains (eg, health care organisation). All domains were also classified in subcategories using a taxonomy for outcome domains, according to clinical, scientific, and patient expertise, adapted from Dodd and colleagues.²⁴ We calculated the number of citations of each domain identified in step 2. We also calculated the proportion of domains common to the three languages, and the proportion of domains cited in only one language.

To ascertain that we achieved a comprehensive list of domains (data saturation), we used a mathematical model to predict the number of new domains that could be identified by adding new participants in the study.²⁵ Data saturation was assessed for each participant group (patients, informal caregivers, and health-care professionals) and by country (France vs other countries) for all domains, for those related to the benefits of treatments, and for the others. All quantitative analyses involved use of R, version 3.3.

Role of the funding source

Funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to publish.

Results

Between April 5, 2018, and Dec 10, 2018, 7373 visitors connected to the study website. 4351 consented to participate in the survey and 3003 participants from 52 countries and five continents completed the questionnaire: 1912 (64%) patients, 464 (15%) informal caregivers, and 627 (21%) health-care professionals (figure 1, appendix 3). Patients and informal caregivers had a higher proportion of women than did health-care

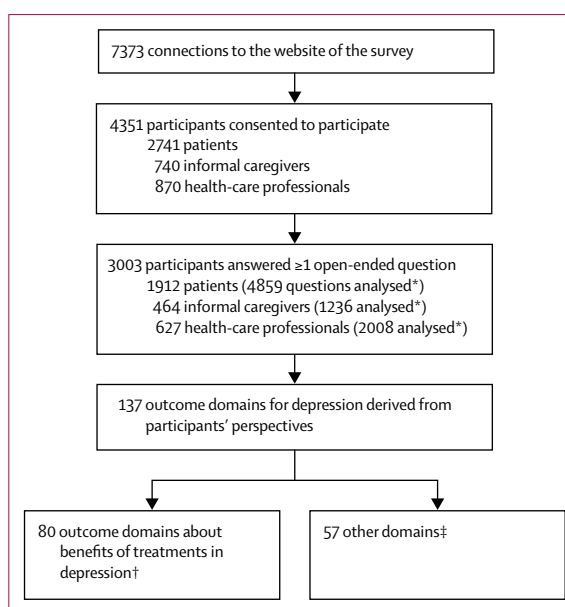


Figure 1: Study flowchart

*Patients answered two–four open-ended questions. Informal caregivers answered three open-ended questions. Health-care professionals answered four open-ended questions. We added the number of open-ended questions answered, for each type of participant. †Results presented in figure 2, table 4, and appendix 3. ‡Results presented in appendix 3.

professionals. All groups (patients, informal caregivers, and health-care professionals) had mostly French-speaking participants from France (appendix 3).

Among 1912 patients, 1421 (75%) were women, with a mean age of 38.3 years (SD 14.4, IQR 18–92), from 40 countries (table 1). According to the PHQ-9, 423 (22%) of 1912 patients met the threshold for likely severe depression at the time of the survey, and 181 (10%) reported bipolar disorder (table 1, appendix 3). Among 464 informal caregivers, 329 (71%) were women, with a mean age of 45 years (SD 17.7, IQR 18–88), from 17 countries (table 2). For 375 (81%) of 464 caregivers, the relative with depression was a member of the close family (parent, children, or sibling). Among 627 health-care professionals, 279 (44%) were psychiatrists, 155 (25%) psychologists, 103 (16%) psychiatric nurses, and 53 (8%) general practitioners, from 33 countries (table 3).

The inductive qualitative content analysis of the 8183 open-ended answers resulted in 137 domains that are of value to participants, classified in two categories: 80 domains to evaluate the benefits of treatment and 57 other domains (figure 2). The list of 80 domains regarding the benefits of treatments is comprehensive because data saturation models showed that at least 90% of all possible domains had been identified for all participant groups and in French and non-French speaking participants (appendix 3). These 80 domains were classified in two sections: reduction of symptoms (64 domains) and improvement in functioning (16 domains; figure 2, table 4, appendix 3).

	Number (n=1912)	Missing data
Gender	..	74 (4%)
Women	1428 (75%)	..
Men	367 (19%)	..
Other	43 (2%)	..
Age, years	..	74 (4%)
Mean (SD)	38.3 (14.4)	..
18–29	615 (32%)	..
30–39	450 (24%)	..
40–49	342 (18%)	..
50–64	350 (18%)	..
65–92	81 (4%)	..
Country	..	28 (1%)
France	1417 (74%)	..
Germany	97 (5%)	..
UK	41 (2%)	..
Belgium	37 (2%)	..
Austria	34 (2%)	..
USA	32 (2%)	..
Other (34 countries)	226 (12%)	..
Duration of education in years	..	74 (4%)
Mean (SD)	16.9 (4.3)	..
Feeling about household income	..	74 (4%)
Living comfortably	359 (19%)	..
Coping	796 (42%)	..
Difficult	408 (21%)	..
Very difficult	188 (10%)	..
Don't know or don't want to answer	87 (5%)	..
Severity of depression score, PHQ-9	..	55 (3%)
Not depressed, <5	279 (15%)	..
Mild, 5–10	320 (17%)	..
Moderate, 10–15	395 (21%)	..
Moderately severe, 15–20	440 (23%)	..
Severe, >20	423 (22%)	..
Duration of the ongoing episode, months	..	0
Mean (SD)	12.2 (8.0)	..
Persistent depression, >24 months		
Yes	276 (14%)	..
Number of previous episodes	..	0
Mean (SD)	2.1 (1.3)	..
Bipolar disorder	..	30 (2%)
Yes	181 (9%)	..
No	1481 (77%)	..
Don't know	220 (12%)	..

(Table 1 continues in next column)

We identified four domains related to autoaggression symptoms: suicidal ideation (695 [23%] of 3003 participants), suicidal attempt (116 [3%]), loss of desire to live (534 [17%]), and self-harm (56 [1%]). Suicidal ideation was the most frequently reported domain (477 [25%] of 1912 patients, 58 [13%] of 464 informal

	Number (n=1912)	Missing data
(Continued from previous column)		
History of suicide attempt	..	31 (2%)
Yes	613 (32%)	..
No	1130 (59%)	..
Prefer not to answer	138 (7%)	..
Follow-up by*	..	236 (12%)
Psychiatrist	1248 (65%)	..
Psychologist	982 (51%)	..
General practitioner	876 (46%)	..
No follow-up	231 (12%)	..
Other (eg, hypnotherapist)	260 (14%)	..
Treatment for depression*	..	87 (5%)
No lifelong treatment	83 (4%)	..
Admission to hospital	496 (26%)	..
Antidepressants*		
Antidepressants only	321 (17%)	..
Antidepressants and psychotherapy	838 (44%)	..
Antidepressants and mood regulator	348 (18%)	..
Antidepressants and neurostimulation	47 (2%)	..
Total on antidepressants	1357 (71%)	..
Psychotherapies*		
Cognitive behavioural therapy	692 (36%)	..
Psychoanalysis	456 (24%)	..
Family psychotherapies	97 (5%)	..
Psychotherapy only (ie, no drugs or neurostimulation)	162 (8%)	..
Total on psychotherapies	1019 (53%)	..
Neurostimulation	50 (3%)	..

Data are n (%) or mean (SD) as stated. PHQ-9=Patient Health Questionnaire 9.
*Total exceeds 100% because a patient could have multiple follow-ups or treatments.

Table 1: Patient characteristics

caregivers, 160 [26%] of 627 health-care professionals). Participants described suicidal ideation as a daily burden of unbearable negative feelings, leading to violence against oneself to stop the suffering. Moreover, struggling against the suicidal idea was reported as a component of guilt and described as exhausting. “The worst in depression is to feel empty, nothing matters, everything is unbearable, the only wish is that it stops at one point, and then comes the daily struggle against yourself, not to commit suicide” (patient, woman, aged 48 years).

We identified 19 domains related to mood and emotional symptoms of depression. The three most frequently reported domains were relief of mental pain (also called psychic or psychological pain in the literature;²⁶ 523 [17%] of 3003 participants), anxiety (521 [17%]), and sadness (515 [17%]). Anxiety was mentioned by most patients (321 [17%] of 1912) and mental pain by informal caregivers (105 [23%] 464), whereas anhedonia was the most frequent

	Number (n=464)	Missing data
Gender	..	54 (12%)
Women	329 (71%)	..
Men	77 (17%)	..
Other	4 (1%)	..
Age, years	..	55 (12%)
Mean (SD)	45 (17.7)	..
Range	18–88	..
Country	..	57 (12%)
France	351 (76%)	..
Austria	13 (3%)	..
Belgium	11 (2%)	..
Other (14 countries)	32 (7%)	..
Feeling about household income	..	87 (19%)
Living comfortably	210 (45%)	..
Coping	112 (24%)	..
Difficult	37 (8%)	..
Very difficult	4 (1%)	..
Don't know or don't want to answer	14 (3%)	..
Employment status	..	56 (12%)
Employed	234 (50%)	..
Not employed	76 (16%)	..
Retired	98 (21%)	..
Relationship with person with depression	..	1 (<1%)
Husband or wife	114 (25%)	..
Father or mother	107 (23%)	..
Son or daughter	100 (22%)	..
Brother or sister	54 (12%)	..
Friend	61 (13%)	..
Other	27 (6%)	..
Living with the person with depression	..	0
Yes	283 (61%)	..
No	181 (39%)	..
Personal history of depression	..	37 (8%)
Yes	163 (35%)	..
No	264 (53%)	..

Data is n (%), unless otherwise specified.

Table 2: Characteristics of informal caregivers

domain mentioned by health-care professionals (267 [43%] of 627). Participants expected a reduction in mental pain from depression treatment, mentioned by 306 (16%) of 1912 patients, 105 (23%) of 464 informal caregivers, and 112 (18%) of 627 health-care professionals. Participants described mental pain as the worst pain ever felt, comparing it with torture, and leading to suicidal ideation to escape this suffering. They also depicted mental pain as unspeakable because it was not understandable by themselves or others. “The emptiness: no feelings anymore. We are psychologically dead” (patient, woman, aged 20 years). “My mother told me ‘I did not know that humans could suffer so much’. She lost any interest. I wished she could

	Number (n=627)	Missing data
Gender	..	109 (17%)
Women	349 (56%)	..
Men	169 (27%)	..
Age, years	..	108 (17%)
Mean (SD)	40.3 (12.3)	..
Range	22–80	..
Country	..	6 (1%)
France	363 (58%)	..
Austria	133 (21%)	..
Germany	36 (6%)	..
UK	16 (3%)	..
Other (29 countries)	73 (12%)	..
Profession	..	2 (0)
Psychiatrist	279 (44%)	..
Psychologist or neuropsychologist	155 (25%)	..
Nurse (psychiatric)	103 (16%)	..
General practitioner	53 (8%)	..
Other	35 (6%)	..
Workplace	..	12 (2%)
Hospital only	292 (47%)	..
Private practice only	113 (18%)	..
Multiple workplaces and other	210 (33%)	..
Professional experience, years	..	4 (1%)
Mean (SD)	11.5 (10.5)	..
Personal history of depression	..	107 (17%)
Yes	152 (24%)	..
No	337 (54%)	..
Prefer not to answer	31 (5%)	..
History of depression for a relative	..	107 (17%)
Yes	344 (55%)	..
No	159 (25%)	..
Prefer not to answer	17 (3%)	..

Data are n (%), unless otherwise specified.

Table 3: Characteristics of health-care professionals

go back to what she was before. I could not recognize her” (informal caregiver, woman, aged 49 years).

We identified 18 domains associated with cognitive symptoms. The three most cited domains were motivation (384 [13%] of 3003 participants), cognitive distortion (275 [9%]), and social interest (227 [8%])—ie, the motivation to seek interpersonal relationships. Patients and health-care professionals mainly expected an improvement in motivation (167 [9%] of 1912, 187 [31%] of 627). Informal caregivers (53 [11%] of 464) expected mostly a reduction in cognitive distortions (ie, biased cognitive patterns, such as catastrophising, all-or-nothing thinking, or overgeneralisation).²⁷ “The negative thoughts were very intrusive, always came in pleasant times to ruin everything” (patient, woman, aged 21 years). “The lack of energy and motivation leads to stopping what you previously enjoyed. Or motivation makes it difficult to

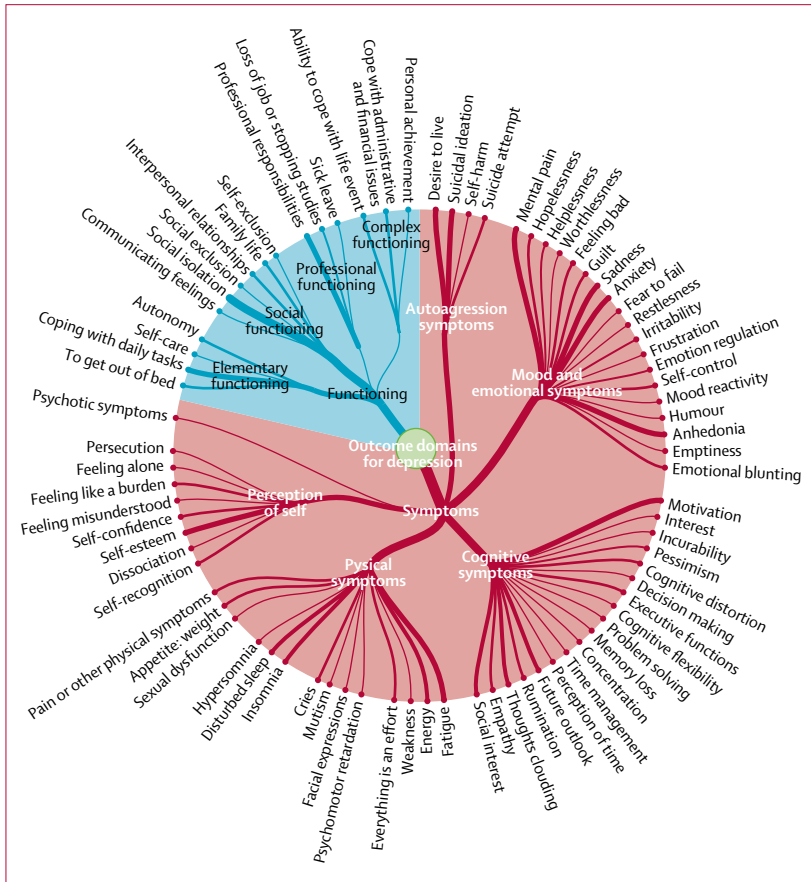


Figure 2: Outcome domains regarding the benefits of treatments in depression
 Dots represent outcome domains regarding the benefits of treatment in depression identified by qualitative content analysis of the open-ended questions asked of 1912 patients, 464 informal caregivers, and 627 health-care professionals. Outcome domains were classified by expert consensus. Width of lines is proportional to the number of spontaneous citations of the domain by all participants as being relevant for depression.

maintain your daily routine and avoid self-negligence. Also, you can feel that your neurological abilities are low (for instance concentration)” (patient, other gender, aged 23 years).

We identified 14 domains associated with the reduction of physical symptoms of depression, such as fatigue (439 [15%] of 3003 participants), low energy (264 [9%]), disturbed sleep (259 [9%]), and insomnia (255 [8%]). Participants mentioned crying as an impairing symptom (122 [4%]). They depicted automatic crying, not associated with emotions or context. They also reported crying as a disruptor of social relationships and a reason to seek professional help. “The worst is my weakness. I have no energy and an abyssal fatigue. I cannot get out of my bed. I cannot do anything in a day, and I can’t see no exit for this” (patient, woman, aged 44 years).

We identified eight domains related to a biased perception of self. Low self-esteem (394 [13%] of 3003 participants) was the most-cited domain, followed by low self-confidence (126 [4%]) and loss of self-recognition (109 [4%]). Participants expected that treatment would

help them to feel themselves again. They described the loss of self-recognition as a negative feeling of having become someone else, with a perception of a personality change (at the individual level) or loss of identity (at a social level). Informal caregivers also mentioned that their relative with depression was difficult to recognise. “I felt I was worthless, useless and I did not deserve to be loved. I always blamed me even when I was doing ok. I hated me always continuously and for no reason” (patient, woman, aged 37 years).

We identified four domains related to improvement of elementary functioning: getting out of bed (91 [3%] of 3003 participants), self-care (46 [2%]), daily tasks (527 [18%]), and autonomy (110 [4%]). Overall, 64 patients, 18 informal caregivers, and nine health-care professionals expected that treatment would allow patients to get out of bed. Participants emphasised the effect of not being able to get out of bed using, for instance, the images of being a dead body, or a dead lift for people who are close to them. “I was not able anymore to assume my daily living and I felt ashamed of my own place, and guilty, so I did not invite anybody home anymore, I was self-isolating” (patient, man, aged 36 years).

We identified three domains related to complex functioning: the ability to deal with administrative or financial issues (132 [4%] of 3003 participants), the ability to cope with daily events requiring adaptive skills (131 [4%]), and personal growth (27 [1%]). Regarding personal growth, participants depicted the remission of depression as an opportunity for further self-development and not just a return to the premorbid state. “This is an invisible illness responsible of a disaster. It’s hard to make things up after 12 years. I feel bitter because of all these wasted years, which could have been efficient (find an interesting job, make friends, find a husband, have children, etc.)” (patient, woman, aged 31 years).

We identified five domains related to improvement of social life. Social isolation was the most evoked domain (541 [18%] of 3003 participants), followed by the quality of interpersonal relationships (154 [5%]) and family life (150 [5%]). Participants expected treatment to restore the ability to fulfil family responsibilities, such as spousal and parenting duties (116 patients, 22 informal caregivers, and 12 health-care professionals). They described the loss of parenting capacity as a painful consequence of depression that led to psychological (eg, guilt) and social distress (eg, conflict with relatives). Some patients also described the loss of parenting capacity as a trigger for seeking professional help. “Social isolation and loneliness are the worst. When I finally recovered and went back to the world, I realized how social isolation made me lose a range of competencies. I had to learn again each single little thing of daily life” (patient, woman, aged 38 years).

We identified three domains related to improvement of professional life, such as the ability to fulfil professional responsibilities (328 [11%] of 3003 participants), avoid sick leave (26 [1%]), and loss of job or discontinuation of

	Verbatim text of patients, informal caregivers or HCPs	Citation number (%)
Suicidal ideation	"The deep and unbearable mental pain makes you think that only suicide can stop the suffering." (patient no age or gender given); "The most difficult to endure are the dark thoughts. We do not live, as depressed people: we survive every single minute of our life." (patient, man, 45 years old); "To control suicidal ideation is mentally exhausting." (patient, man, 24 years old); "To have suicidal ideation when you have two little kids is the worst to live with" (patient, woman, 33 years old)	Patients: 477 (25%) of 1912; ICs: 58 (12.5%) of 464; HCPs: 160 (26%) of 627
Mental pain	"Moral suffering made my daily life unbearable. I had to endure physical pain in my life but I consider them insignificant in comparison to depression." (patient, woman, 47 years old); "Depression is an extreme pain that is really difficult to understand by our relatives (it can't hurt because it is NOT physical). The worst is the loneliness because of this pain, when people can't bear your complaining about suffering anymore" (patient, woman, 22 years old); "The psychological suffering is a torture for him." (informal caregiver, woman, 50 years old, talking about her brother)	Patients: 306 (16%) of 1912; ICs: 105 (23%) of 464; HCPs: 112 (18%) of 627
Motivation	"The lack of energy and motivation leads to stopping what you previously enjoyed. Of motivation make it difficult to maintain your daily routine and avoid self-negligence. Also you can feel that your neurological abilities are low (for instance concentration)" (patient, other gender, 23 years old); "The inertia, the lack of motivation, the lack of meaning of life, and each morning, the same question: 'Why should I go out of my bed?'" (patient, woman, 30 years old); "Treatment of depression should ameliorate the loss of motivation. They've lost all motivation, except for committing suicide." (HCP, psychiatrist, woman, 30 years old)	Patients: 167 (9%) of 1912; ICs: 30 (6%) of 464; HCPs: 187 (30%) of 627
Crying	"My father brought me to the doctor. I was 24 years old. I could not sleep anymore, I was crying every time, even when looking at birds, and I had a strong anxiety". (patient, woman, 50 years old); "For me the worst was being unable to control crying in public and the way people see you afterwards, especially professionally: you lose credibility." (patient, woman, 43 years old); "My symptoms were exclusively physical. I was told that it was a typical 'men depression', with agitation, sleep disturbance, loss of appetite. I never felt 'empty' or sad or tearful" (patient, man, 38 years old); "I was struggling to get out of bed, not eating, not caring for myself, not washing etc. I couldn't go to work. I felt sick, I was crying and I had no energy." (patient, woman, 50 years old); "The worst with depression is the isolation. When I don't want to go out of my room, when the 50 meters between my bed and my mailbox were impossible to walk." (patient, woman, 52 years old)	Patients: 111 (6%) of 1912; ICs: 6 (1%) of 464; HCPs: 5 (1%) of 627
Self-recognition	"The worst is the feeling of not being yourself anymore, I'm a wreck (I used to be a fighter and now I'm a careless complainer)" (patient 932, woman, 24 years old); "I decided to seek for medical help the day I yelled at my husband. It was after several days of being unable to go to work because I could not concentrate and I just wanted to stay hidden at home. Some behaviours I'm not familiar with." (patient, woman, 35 years old); "My mother told me 'I did not now [A: OK to correct to "know"?] that humans could suffer so much'. For her the worst was to have the feeling of being mad, she lost any interest. I wished she could go back to what she was before. I could not recognise her." (informal caregiver, woman, 49 years old)	Patients: 73 (4%) of 1912; ICs: 5 (1%) of 464; HCPs: 31 (5%) of 627
To get out of bed	"I was struggling to get out of bed, not eating, not caring for myself, not washing etc. I could not go to work. I felt sick, I was crying and I had no energy." (patient, woman, 50 years old); "The worst with depression is the isolation and also when I don't want to get out of my room, when the 50 meters between my bed and my mailbox were impossible to walk." (patient, woman, 52 years old); "I feel disabled: I am not even able to get out of my bed" (patient, man, 41 years old)	Patients: 64 (3%) of 1912; ICs: 18 (4%) of 464; HCPs: 9 (1%) of 627
Family life	"Lack of motivation, not being able to start things, mental pain, anxiety were bad. But what made me suffer the most was not anymore being able to care about my children. I drop them off at school just to get rid of them. I had the feeling that I was not a good mother, that I have lost the feeling of loving my children." (patient, woman, 48 years old); "I decided to see a doctor for my children who were very young at the time—wanting to love and laugh with them/enjoy life with them again but also not let them be affected by what I was going through. I had the fear that I would sink to the point of no return or remain in constant state of depression without help/support. I wanted to get my life back not just struggle to get by each day." (patient, woman, no age given)	Patients: 116 (6%) of 1912; ICs: 22 (5%) of 464; HCPs: 12 (2%) of 627
Professional responsibilities	"The fear was always here: the fear of acting, of thinking (I have very dark thoughts sometimes, or in the contrary I had no thoughts anymore). The fear when you are not even able to cry because your body turned into an automat. These behaviours lead to an important distance with my family and friends and to the deterioration of the quality of my work (shortened attention time, an extreme fatigue)." (patient, no gender or age given); "The loneliness is also a consequence of the sick leave: during that time, kids are at school, friends and family at work and it is difficult to find something to do. Moreover, the intellectual and emotional weakness of depression let us as zombies, which can lead to conflicts. The family often 'forget' that we are sick, they want us to go back to work because they are afraid for our professional future, sometimes confusing depression with laziness (but I'm aware of the burden we are for our relatives)." (patient, man, 44 years old)	Patients: 230 (12%) of 1912; ICs: 19 (4%) of 464; HCPs: 79 (13%) of 627
Administrative/ financial issues	"The loss of income was very high: first you start to lose a part of your wage, then the wage itself and at the end the unemployment benefit. And the disabling benefit will never cover this loss." (patient, man, 54 years old); "I had to help her not to lose her job, and to renew her paper (she was an immigrant). It was tricky to have a balance between avoiding her isolation while respecting her privacy." (informal caregiver 244, woman, no age given, taking care of a friend)	Patients: 73 (4%) of 1912; ICs: 48 (10%) of 464; HCPs: 11 (2%) of 627

The number (%) of spontaneous citations of the outcome domains is reported for each type of participant. ICs=informal caregivers. HCPs=health-care professionals.

Table 4: Verbatim text for patients, ICs and HCPs for outcome domains

studies (50 [2%]). Participants depicted depression as a rupture in life trajectories (eg, loss of job) or social or psychological distress (eg, anxiety, low self-esteem, stigmatisation, and impoverishment). "I could not go working, I could not even get out of my home. I had no

motivation for nothing. I felt I was in the depth of a dark hole, naked and alone" (patient, woman, aged 26 years).

We also identified 57 other domains covering medication efficacy, treatment safety, facilitation of psychotherapeutic approaches, medical care organisation, development of

other therapeutic approaches, the ability of the patient to seek help, and the social representation of depression (appendix 3). Among 3003 participants, the three most-cited domains were to raise awareness of society about depression (563 [19%]), reduce the stigma of depression (depression is not a weakness, sign of laziness or lack of courage; 408 [14%]), and improve access to a psychiatrist (302 [10%]). Patients also reported the difficulty of having insight into their own depression (320 [17%] of 1912). Informal caregivers defended the importance of talking with depressed patients: they claimed that psychiatrists do not support patients enough (65 [14%] of 464), brought up as a consequence the importance for patients to have someone (family, friend) to talk to (61 [13%]) and asked that psychotherapy be mandatory (57 [12%]). Health-care professionals expected the treatment to bring patients back to a premorbid state (126 [20%] of 627) and wanted improved recognition of depression as a serious illness, not only by the whole society (105 [17%]), but also by the patient's own family (79 [13%]). Data saturation was reached for patients, informal caregivers, and health-care professionals, but not within the specific groups of non-French informal caregivers and French and non-French health-care professionals. "I had to hide my depression not to make my relatives afraid, or not to be considered as crazy" (patient, woman, aged 42 years). "People who do not understand depression and tell me that if I want to, I can feel better, that I only need to take some fresh air" (patient, man, aged 35 years). "It is difficult to consider the symptoms as the result of a disease and not as a weakness. This is why I felt guilty and ashamed of being sick" (patient, woman, aged 31 years).

Among the 80 domains regarding the benefits of treatments identified in our study, 57 (70%) were cited in all three languages. In total, 19 (24%) domains were cited by only French-speaking and German-speaking participants or French-speaking and English-speaking participants. Four domains were cited by only French-speaking participants: "everything is an effort" (100 [4%] of 2425 participants), "decision making" (27 [1%]), "cognitive flexibility" (five [$<1\%$]) and "time management" (19 [1%]). The discrepancy between languages could be associated with the larger sample of French-speaking participants. Among the 57 other domains, 36 (63%) were cited in all three languages and 14 (25%) in two languages.

Discussion

With the qualitative content analyses of open-text answers from 3003 patients, informal caregivers, and health-care professionals from 52 countries, we identified 80 domains to assess the benefits of depression treatment that matter to these three groups and 57 other domains important for clinical practice, health care organisation, and social change.

To our knowledge, this is the first study to provide the list of the domains that matter to patients, informal caregivers, and health-care professionals. Some of the domains are

not or rarely measured in trials, such as mental pain, which was one of the most frequently cited domains. A meta-analysis of 42 studies showed an association of mental pain with suicidal behaviours.²⁸ However, this domain is not measured in any of the seven most commonly used scales (Hamilton Depression Rating Scale [HDRS], Beck Depression Inventory [BDI], Montgomery and Asberg Depression Rating Scale [MADRS], Inventory of Depressive Symptomatology [IDS/QIDS]), Zung-Self-rating Depression Scale [Zung], Center of Epidemiologic Studies-Depression scale [CES-D], and PHQ-9).¹² Similarly, we identified functioning (eg, capacity for patients to live a family life, get out of bed, be able to work) as a group of domains that matter to participants. However, functioning is not measured in six of the most used depression-rating scales (BDI, MADRS, IDS/QIDS, Zung-SDS, CES-D, and PHQ-9).¹² A cursory review of 90 meta-analysis of trials found that fewer than 5% of them reported functional outcomes despite several calls by researchers in the 2000s.^{12,14,29,30}

Since domains were generated from the fine-grained descriptions of participants' lived experience of depression, this study adds knowledge to their definition. Taking suicidal ideation as an example, participants considered several relevant dimensions, such as the intensity of suicidal ideation, the effort made to fight these ideas, and the emotional consequences (fear, guilt, shame, and psychological distress). These components do not align with how suicidal ideation is measured in common depression scales (or in the DSM-5 diagnosis of major depressive disorder), which highlights the importance of qualitative work involving stakeholders.

One strength of the study is the diversity of participants in terms of sociodemographic and health status (eg, countries, gender, age, socioeconomic levels, severity). In the answers to open-ended questions, some patients with depression reported comorbid psychiatric disorders (eg, anorexia nervosa, borderline disorder, schizophrenia) or comorbid chronic diseases (eg, fibromyalgia, diabetes mellitus, multiple sclerosis). We did not exclude these patients because in reality they will also receive treatment for their depression. A second strength of our study is that domains were generated from the participants' lived experience of depression. The use of open-ended questions gave room for free expression, with minimal disruption in the process of collecting data.^{20,23} A third strength was the participatory approach of our study. The whole research process was a collaboration between researchers, patients, health-care professionals, and informal caregivers. For example, one member of the research team (ST) is an experienced expert who has lived through several episodes of unipolar depression and has received various treatments. She participated in the conception of the research, development of the questionnaire, analysis of data, and writing of the paper.

A limitation is the non-representativeness of our sample regarding nationality. Our sample was mainly

composed of French, British, North American, Austrian, and German participants because the survey was available in the three corresponding languages and we disseminated the survey from these countries. Despite an imbalance in the number of French-speaking participants, in comparison to other participants, data saturation was reached in all subgroups except non-French speaking informal caregivers, who proved difficult to recruit. However, our survey recruited mainly participants from high-income countries in Europe and North America, and people from other cultures and contexts might experience depression in different ways, thereby leading to some overlooked domains. Further research in other cultural areas should complement our findings.

A second limitation is that the diagnosis of depression, the severity of the depressive episode (PHQ-9), and the history of depression (eg, number of episodes, suicide attempts) are self-reported by participants, which can lead to information or recall error in the data. A third limitation is the restriction to patients, informal caregivers, and health-care professionals, although we could have enrolled other stakeholders, such as researchers or trialists. However, considering the scarcity of evidence about outcomes that matter to the first three groups and the fact that they are the ones who have to take or prescribe the treatment, we chose to focus on these populations. A fourth limitation is that we did not involve professional translators in the research process, which could have been helpful particularly when merging the three codebooks. The four coders and the patient all spoke English (but only one as the mother tongue), three spoke French, and two spoke German.

Our findings do not cover comprehensively domains assessing the safety of treatments. We formulated the questions of the survey to identify outcome domains regarding the benefits and not the harms of treatment. Asking patients about their expectations for treatments makes sense, but asking them about the safety of these treatments would have required them to anticipate potential adverse events.

The main use of this study is to set the first step of the development of a COS for trials in depression. This COS will ensure that trials use outcomes relevant to all stakeholders across different countries, cultures, and contexts. Previously, Obbarius and colleagues proposed a set of standardised outcomes for assessing the quality of care for depression and anxiety by merging the results of a systematic review and the opinion of 24 experts (ten health-care professionals, ten researchers, two coordinators, and two patient advocates).³¹ Their set included the PHQ-9 for symptoms, the supplementary question of the PHQ-9 to assess functioning, two developed items for time to recovery, and one developed question for side-effects. However, the small sample size (only two patients) limited the generalisability of the findings and the validity of these choices. Among four studies about patient preferences for medication-associated outcomes in

depression, only one included patients (and only eight) to generate outcomes.³² The other relied exclusively on reviews of the literature. Our work, involving a large population of stakeholders, enabled the identification of domains beyond the classical domains used by researchers and avoided the perpetuation of research habits. Moreover, by assessing data saturation, we ensured that our results were comprehensive. Therefore, this study is a proof of concept of a new method for COS development allowing for the involvement of a large number of stakeholders internationally to identify outcome domains.¹⁷ Doing this study with participants living with depression suggested that it should be feasible for other conditions because depression is a disorder with symptoms that can inhibit participation in a survey with open-ended questions (eg, insufficient motivation, fatigue, worthlessness, diminished social participation). Moreover, our sample included a considerable proportion of patients with severe depression, which suggests that the burden of the survey was acceptable for participants. Future steps in the development of a COS for depression will be the selection of a few core outcome domains by all relevant stakeholders and the identification of relevant tools to measure these domains.

Further use of the study is grounded in the panorama or depression it gives, which can help all stakeholders (health-care practitioners, researchers, policy makers, etc) to better understand what living with depression is and the main issues patients are dealing with.

Contributors

All authors searched the literature. ACh, ST, EF, GG, ACi, VTT, and PR designed the study. ACh and VTT designed the questionnaire. ACh, VTT, and PR designed the figures. ACh, VTT, EI, GG, and ACi collected the data. ACh, CLB, BT, AT, and ST analysed the data. All authors interpreted the data. ACh wrote the first draft. All authors edited the manuscript.

Declaration of interests

ACi received research and consultancy fees from the Italian Network for Paediatric Trials, CARIPLO Foundation, and Angelini Pharma. All other authors declare no competing interests.

Data sharing

Deidentified quantitative data will be shared on reasonable request to the corresponding author.

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