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Choice of Treatment with Antidepressants: Influencing Factors

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Abstract: Depressive disorders place a large burden on patients and on society. Although efficacious treatment options for unipolar depressive disorders exist, substantial gaps in care remain. In part, the challenge lies in the matching of individual patients with appropriate care. This is complicated by the steady increases in the variety of antidepressants available in the market. The goal of this study is to highlight the decision processes in the selection of antidepressants by clinicians, given that most treatments have similar clinical effectiveness profiles.

We conducted a systematic literature review of studies that referred to the decisions surrounding treatment with antidepressants for the treatment of non-psychotic unipolar depression. Our analysis of the literature reveals that the choice of treatment is based on a variety of factors, of which clinical evidence is only one. These factors can be categorized into clinical factors such as illness and treatment characteristics, individual factors such as patient and physician characteristics, and contextual factors such as setting characteristics, decision supports and pharmacoeconomic aspects.

Illness characteristics are defined by the type and severity of depression. Treatment characteristics include drug properties, efficacy, effectiveness and favorable as well as unintended adverse effects of the drug. Examples for patient characteristics are co-morbidities and individual preferences, and physician characteristics include knowledge, experience, values and beliefs, and the relationship with the patient. Treatment guidelines, algorithms, and most recently, computational supports and biological markers serve as decision supports.

Keywords: Antidepressants, decision making, pharmacoeconomics, treatment algorithm, serotonin reuptake inhibitors, tricyclic antidepressants.

1. INTRODUCTION

Depressive disorders are common conditions that place a large burden on patients and on society in terms of both the illness itself, as well as costs. The worldwide twelve-month prevalence rate of depression may be estimated to 5% or even higher, and the lifetime risk for depression is about 15%. Depression is a potentially fatal disorder, where the lifetime risk for suicide is approximately 2%. The costs of depression have doubled over the past decade. Costs are high due to both direct medical costs, as well as indirect costs, such as the productivity loss from sick leave, early retirement or adverse events during the treatment of depression [1, 2].

Despite increasing numbers of treatment options, substantial gaps in care remain. These could be attributed to three core problems: (i) only about 50% of depressions are correctly diagnosed by the treating physician, (ii) fewer than 50% of the correctly diagnosed patients receive adequate treatment with adequate doses and treatment duration, and (iii) fewer than 35% who receive an adequate treatment achieve remission with the first applied antidepressant drug [3].

From the perspective of the clinician, the choice of treatment is particularly challenging for a number of reasons. None of the available treatments is a panacea for all patients, the menu of options is bewilderingly long, and clinical evidence does not give a solid basis for selection. This paper identifies factors that influence how physicians select a treatment for individual patients from the menu of available antidepressants. The choice between drugs versus alternative therapy is mentioned, but is not addressed extensively in this paper.

Since the discovery of imipramine in 1956, the number of antidepressants available on the market has been increasing steadily, and more are waiting for approval by central decision making bodies such as the United States (US)-American Food and Drug Administration (FDA) and/or the European Medicines Agency (EMEA). Most antidepressants tend to show similar clinical effectiveness [4, 5], which is typically established for average patient populations [6]. Even the extensive Sequenced Treatment Alternatives to Relieve Depression study (STAR*D) which enrolled more than 4,000 patients was unable to provide specific significant differences in treatment efficacy at any study level [7], and additionally showed equality of psychotherapy and antidepressant treatment [8]. Table **1** provides an overview of the 12 most commonly prescribed antidepressants in the US as well as the frequency of treatment response under this medication, side effects and specific properties [9].

The medical ideal is that treatment of illness be based on illness characteristics and clinically proven guidelines. All physicians should adhere to the same scientific standard, and therefore a particular patient should receive the same treatment regardless of provider and location [10]. In the case of mental illness, clinical guidelines to the use of pharmacotherapy are broad and imprecise: the main criterion for selecting drug based therapy for depression is the severity of the condition, and the selection of the drug is to be based on the profile of adverse reactions. Guidelines also recommend that drug dosage must be sufficiently high, and that earlier intervention generally leads to speedier results [11, 12].

Additionally, the reality of drug treatment often deviates from these already spongy guidelines. Treatment of depression by psychiatrists or general practitioners (GPs) differs from the textbook standards in terms of treatment selection, dosage, time course, age adaptation, polypharmacy and the management of adverse events [11]. Dosage is often too low [13], and older drugs are often prescribed as first line therapy despite their dangerous or even fatal adverse effects, because they are less costly to patients and the insurance companies [14].

There is little scientific evidence on the basis of which individual patients can be matched with the appropriate treatment. The clinical guidelines that do exist despite insufficient evidence are frequently violated by GPs and psychiatrists. The selection of

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Table 1. Effectiveness and Tolerability of the Most Commonly Prescribed Antidepressants in the US According to the Consumers Union of United States 2011 [9]

Antidepressant	Response to Treatment[1]	Discontinuation Because of Side Effects[2]	Comments/Special Notes[3]
Bupropion	55-70%	6-8%	Lowest rate of sexual side effects Risk of seizures at high doses
Citalopram	55-70%	5-9%	None
Desvenlafaxine	55-70%	6-22%	May increase blood pressure
Duloxetine	55-70%	3-13%	Has been associated with liver failure, including some cases that were fatal May increase blood pressure
Escitalopram	55-70%	3-10%	FDA approved for use by teenagers
Fluoxetine	55-70%	7-14%	FDA approved for use by children and teenagers
Fluvoxamine	55-70%	Insufficient data	Not FDA approved for treatment of depression, used "off label" for this illness Higher rate of side effects and drug interactions compared with several other SSRIs in one key study[4]
Mirtazapine	55-70%	10-17%	May have faster onset of action Higher risk of weight gain
Nefazodone	47-59%	Insufficient data	Reports of liver failure leading to death or liver transplant
Paroxetine	55-70%	7-16%	Higher risk of sexual side effects compared with other antidepressants Higher risk of sweating
Sertraline	55-70%	7-14%	Higher rate of diarrhoea
Venlafaxine	55-70%	9-16%	Substantially higher rate of nausea and vomiting May increase blood pressure and heart rate

[1]Response defined as at least 50 percent symptom reduction in depression rating scales.
[2]Numbers are the lower and upper quarter percentile of discontinuation rates from studies.
[3]Based on multiple studies and combined analysis of studies, or from the drug's product label information. Statements made in reference to all other drugs listed except where noted. List is not intended to be comprehensive.
[4]The other SSRIs were fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft).

treatments at the individual patient level is driven by a variety of factors outside of the scope of clinical guidelines. This may contribute to the low success rate of treatments for depression. It may also contribute to the high costs of care for depression, the lack of a standardised methodology for economic evaluations, and a general non-acceptance of economic evidence as an important factor in decision making.

This paper provides a functional framework for understanding the determinants of physicians' treatment selection, as discussed in the literature. The next section describes the methods used in the selection of the literature, followed by a summary of the literature, an example for the application of the obtained results into a treatment algorithm for depressed inpatients and the discussion of the findings. We classify the determinants of choice into seven dimensions, each of which is discussed: illness characteristics, treatment characteristics, patient characteristics, physician characteristics, setting characteristics, decision supports and economic aspects.

2. METHODS

A literature review was performed using the Medline/Pubmed database. Search terms included "antidepressive agents" OR "antidepressants" AND "decision". At the time of the search (May 17th, 2011) 713 titles were returned. All abstracts were scanned for relevance using the following inclusion criteria: referred to antidepressant treatment decision and referred to non-psychotic unipolar depression. 183 articles (original studies, as well as review articles, guidelines and comments) were included for detailed review.

Articles were excluded if they referred exclusively to the treatment of disorders other than unipolar depression, such as bipolar disorder, dependence syndromes (above all smoking cessation), pain disorders including polyneuropathia, neuropathic pain, migraine, neuralgia, myalgia and functional abdominal pain, anxiety disorders, panic disorder, attention-deficit hyperactivity disorder (ADHD), schizophrenia and delusional disorders, dementia and other organic mental disorders, Parkinson disease (PD), narcolepsy, Tourette Syndrome (TS), restless legs syndrome (RLS), neurotic and stress-related disorders such as post-traumatic stress disorder (PTSD), adjustment disorder, acute stress reaction and obsessive–compulsive disorder (OCD), impulsive behaviour, sleep disturbances and insomnia, tinnitus, eating disorders, fibromyalgia, premenstrual dysphoric disorder (PMDD), menopausal symptoms, hot flashes, postmenopausal problems, erectile dysfunction, ejaculation failure, urinary incontinence, enuresis, interstitial cystitis, masticatory system dysfunction, irritable bowel syndrome (IBS), ulcerative

colitis, atopic dermatitis, human immunodeficiency virus (HIV) infection and disease, fatigue, and scoliosis. Further exclusion criteria included studies being related to suicidality and self poisoning or to therapy options exclusively other than antidepressants such as electroconvulsive therapy (ECT) or homeopathy. We also excluded articles related to neuropsychological research and MRT studies, to animal studies, to pure pharmacological and toxicological aspects of antidepressants or related to several other aspects not related to the decision for an antidepressant in unipolar depression. Additionally, we supplemented the relevant articles with additional literature found in subsequent searches.

3. RESULTS

The determinants of choosing a treatment for depression as discussed in the literature can be classified into seven broad categories. Table **2** summarizes categories and individual determinants within them which will be explained in the following paragraphs.

In part, the decision reached depends on the goals of treatment, about which there seems to be consensus; given the goal, the determinants of treatment choice relate to the characteristics of the disease and the treatment, to the patient and his physician, to the treatment setting including alternatives for antidepressants, and to available decision support tools and pharmacoecnomic data.

3.1. Goals of Antidepressant Treatment

The main goals of treatment with antidepressants as discussed in the literature include achieving maximum remission, minimisation of side effects, and reduction of costs [15-18]. Remission is associated with improved day to day function and a better prognosis [19]. The maximization of remission is supported by the objectives of attaining full and sustainable remission of symptoms [17], preventing relapse [18], prolonging of time without depression [15], increasing adherence to therapy [16], improving the quality of life, and taking advantage of additional positive drug effects [5]. The minimization of side effects is a direct goal, and also supported by the objective of maximizing the adequacy of treatment [5]. The reduction of costs is supported by the objectives of lowering direct health care costs via e.g. reducing hospitalization and readmission rates, and via lowering indirect costs that arise due to losses in productivity [5, 15].

3.2. Decision Criteria and Influencing Factors

3.2.1. Illness Characteristics

In the absence of sufficient knowledge as regards the neurobiology of depression, the best system of diagnosis and classification remains uncertain. Researchers and clinicians use both dimensional and categorical approaches in investigational studies and clinical practice [20]. Classification attempts of putative depressive subtypes have occurred on the basis of symptom profile according to atypical, melancholic, psychotic [20], severity [21] and chronicity [20] of illness, the presence of circadian or other cyclical mood fluctuations [22], or of physical symptom, such as headache, lumbago, abdominal pain, dizziness, sleep disturbance, appetite loss. Diagnostic differentiation has also been sought according to age of onset [23, 24] and presumed aetiology, especially in the context of medical illnesses. However, as yet, no satisfactory or universally accepted taxonomy has emerged.

It is recommended by the recent literature which is summarized in a review of Malhi *et al*. [20] to consider three depressive subtypes for choosing a psychopharmacological treatment, the atypical, melancholic and psychotic one and the classification according to the degree of severity as it is conceptualized in the 10th revision of the international classification of diseases (ICD-10).

The *atypical* subtype is characterized by mood reactivity and two or more of the following features: significant weight gain or

Table 2. Factors Influencing the Choice of Antidepressants

Category of Choice Criteria	Examples
Disorder	Subtype
	Severity
	Course of treatment
Treatment	Efficacy
	Effectiveness
	Ranking among other ADs
	Other favourable effects
	Toxicity
	Side effects
	Mechanism of action
	Drug interactions
	Ease of use
Patient	Previous use of antidepressants
	Comorbidities
	Age
	Gender
	Ethnic group
	Body weight
	Pregnancy
	Breast feeding
	Attitudes
	Health insurance
	Income in relation to the costs
Physician	Specialty
	Knowledge
	Experience
	Beliefs
	Preference of shared decision making
	Thinking about the patient, depression and treatment alternatives
	Ideological resistances against pharmacotherapy and ethical values
Setting	Inpatient/outpatient
	Technical facilities
	Resources and structural characteristics
	Alternative treatment options
Decision supports	Biomarkers
	Artificial neural networks
	Computerized documentation and expert systems
	Guidelines
	Algorithms
Pharmacoeconomics	Cost-effectiveness data
	Cost-utility data
	Assessment of health technology appraisal (HTA) agencies

increased appetite, hypersomnia, leaden paralysis, long-standing pattern of sensitivity to interpersonal rejection. SSRIs are considered preferable as first-line. But MAOIs appear to be more effective compared to SSRIs or TCAs in these patients and can be considered in cases of non-response, but are not recommended as an initial option because of increased risk of adverse effects, contraindications and dietary restrictions as explained before [20, 25].

The *melancholic* subtype is characterized by psychomotor changes and somatic symptoms. Melancholic depression has a lower placebo response rate compared with depression without melancholic features, suggesting lower rates of spontaneous recovery and a greater need for active treatment. Evidence suggests that TCAs and dual acting agents have superior efficacy when compared with SSRIs [26]. Depression with melancholic features appears to respond well to a combined antidepressant and ECT treatment [27].

The *psychotic* subtype is defined by depression accompanied by delusions or hallucinations that are usually, but not always, mood congruent. TCAs appear to be more effective than other antidepressants in treating psychotic depression. Combining an antidepressant with an antipsychotic has been shown to be more effective than an antidepressant alone; some but not all studies support the benefit of this combination [28]. Antipsychotic monotherapy is not as effective as a combination of antipsychotic and antidepressant. ECT is an effective treatment alternative [20]. As this article mainly focuses on depression without psychotic features we do not want to go into detail with regard to this issue.

Furthermore, the ICD-10 categories of depression: mild, moderate or severe have impact on the guidelines for treating depression. In the guidelines, mild depression has the most variance in treatment recommendations; some, but not all guidelines suggest that it may resolve with exercise or watchful waiting, but psychotherapy or antidepressants could be used if initial efforts fail. First-line treatment recommendations for moderate major depressive disorder include antidepressant monotherapy, psychotherapy, and the combination of both. And severe depression may require the combination of an antidepressant and an antipsychotic, electroconvulsive therapy, or the combination of an antidepressant and psychotherapy according to these guidelines [29].

Response or non-response to the first applied antidepressant influences the choice for the next treatment step. A patient might, for example not respond to the first SSRI [30]. Raising the dosage of the current drug or switching to an antidepressant from a different pharmacologic class are possible strategies [30]. Other strategies are augmentation strategies with lithium, thyroid hormone, pindolol, psychostimulants and second-generation antipsychotics [31]. Evidence in these decisions is low but will be discussed within the section "decision supports". Although we present this issue under the heading "illness characteristics", one might also argue that the "history of treatment" is one of the treatment characteristics.

3.2.2. Treatment Characteristics

Treatment characteristics include the features of the drug. Drug features are efficacy, effectiveness, toxicity, side effects (positive and negative), raking among other drugs, the mechanism of action, drug interactions, ease of use and availability of alternatives.

Given that remission is a primary goal of treatment, the efficacy of a drug to achieve remission should be a primary criterion physicians use when choosing an antidepressant [32]. The efficacy of antidepressants in general is well established by a high number of randomized controlled trials (RCTs). A large proportion of trials compare the study drug to a placebo, as required by the FDA or the European EMEA [33-38]. In this respect, we again refer to Table **1** which provides an overview regarding effectiveness and tolerability of antidepressants the most commonly prescribed antidepressants in the US. With respect to treatment response, one has to take into account that these rates are derived from RCTs and not from real world-approaches. Therefore, these rates may be higher than rates that could be obtained in the typical in- or outpatients.

Unfortunately the current state of evidence does not support a universally accepted ranking of antidepressants by efficacy, as the results of single RTCs and meta-analyses are inconsistent. As mentioned above, most of the commonly prescribed antidepressants show similar response rates in RCTs. If clinical evidence was to be the primary criterion, a physician would be forced to make judgements on the basis of conflicting or methodologically weak studies. As an example, a ranking is provided in a multiple-treatments meta-analysis (accounting for both direct and indirect comparisons) of 12 new-generation antidepressants for major depression. The ranking suggests that mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine [39]. The ranking is criticized in the literature on methodological grounds, and the authors are accused of ignoring biases in clinical trials, using unpublished data, and failing to include relevant studies. Nevertheless, this study is one of the best published, most cited and most authoritative papers in recent years.

Studies of efficacy are insufficient to support clinical decision making for the following reasons: the nature of clinical evidence; unintended effects; and drug characteristics, including interactions with other drugs, ease of use, and the mechanism of action. First, efficacy is established at the population level and the most efficacious drugs may or may not be most appropriate for individual patients [6]. This is a problem with clinical research in general, not specific to antidepressants. Second, there is the well known difference between efficacy as established in strict clinical trial settings, and effectiveness in the field. In real life, medications are used in doses and frequencies never studied and in patient groups never assessed in the trials. Drugs are used in combination with other medications that have not been tested for interactions. In most cases, effectiveness is lower than efficacy. For example, a post hoc analysis of the STAR*D study found that 78% of the studied patients would have been excluded from a clinical trial on the basis of strict inclusion criteria [40]. Those STAR*D patients who met RCT inclusion criteria had greater likelihood of remission than those more representative of the vast majority seeking care (34.4 vs. 24.7% remission rate), which would lead to a trial efficacy measure greater than an effectiveness measure as it has to be considered for treating a real-world patient.

Another drug-related factor that steers the therapeutic decision are the intended and unintended effects of drugs, which can be positive or negative, safety issues, toxicity and tolerability [41-43]. Intended and favourable benefits of antidepressants can include an improvement of sleep by tricyclic antidepressants (TCA) or mirtazapine [44], or the induction of appetite and weight gain in patients experiencing depression induced weight loss [45]. Unintended adverse effects of TCAs can include sedation, anticholinergic and cardiovascular effects such as prolonged QT interval and induction of torsade de pointes, or weight gain when not desired [4, 45-47]. Selective serotonin reuptake inhibitors (SSRI) may induce the syndrome of inappropriate antidiuretic hormone secretion, bleeding, serotonin syndrome, serotonin-discontinuation syndrome, adverse pregnancy and neonatal effects or sexual dysfunction and weight gain [1, 48, 49]. MAOIs may cause postural hypotension, and when foods containing tyramine are consumed, the patient may suffer from hypertensive crisis [50]. The selection of this drug depends on the ability of the patient to control tyramine intake in their diet. Sedation or appetite stimulation may be useful early in treatment, but can cause problems later in treatment. Sexual dysfunction is of little consequence for a patient suffering from an acute depressive episode but may interfere with social functioning and well-being after recovery. In the long run, sexual dysfunctions are a principal reason for nonadherence leading to relapses to the depressive disorder [51].

The effects of antidepressants on suicide risk must be a key consideration in the selection of drugs. On the one hand, antidepressants have been suspected to increase the risk of suicide in individuals [52]. The increase of the suicide risk seems to be most relevant when starting an antidepressant medication. And moreover, some patients might even attempt suicide by overdosing on the prescribed medication [53].

On the other hand, a negative association between antidepressant use and suicide has been found both on the aggregate and at the individual levels [54], leading some researchers to conclude that the increased use of antidepressants has contributed to the worldwide reduction in suicide rates [55]. One can assume that antidepressants, in general, prevent patients from suicide, although there may be an increased risk for suicide during the start of an antidepressant medication for an individual patient given the frequently reported mismatch between increased motivation but persistent low mood at treatment initiation. However, there is a clear need for further studies between the relationship of antidepressants and suicide risk.

The issue of antidepressant-induced suicide associated with the beginning of an antidepressant therapy was most vehemently discussed for children and adolescents, and the question arouse whether specific antidepressants differ with regard to the associated risk of suicide. As an example, a 9-year cohort study using population-wide data from British Columbia tracked new users of antidepressants who were 10 to 18 years of age with a recorded diagnosis of depression. Hospitalization attributable to intentional self-harm and suicide death was recorded and evaluated. There were no meaningful differences between patients using fluoxetine with citalopram, fluvoxamine, paroxetine, and tricyclic agents [52] meaning that the suicide risk does not seem to be a criterion for the choice between different antidepressants.

Drug characteristics also include possible drug interactions [56, 57]. Depressed patients, especially elderly persons, often take several medications prescribed by other physicians. Some antidepressants can induce or inhibit liver enzymes necessary for the metabolism of many medications, thereby lowering or raising the blood levels of these medications to subtherapeutic or dangerous levels. It is often possible to plan for these interactions and to monitor medication levels.

The ease of use in antidepressant treatment plays an important role in drug selection, too, as it can affect patient compliance. The ease of use depends on the form of administration (oral versus intravenous), and the tablet formulation [58, 59]. Some medications, such as bupropion, must be taken several times a day when used at higher dosages. Therefore, an extended-release formulation of the drug has been developed. The dosage of others, such as nefazodone, may need to be slowly increased over several days or weeks. In both instances, patients' compliance may be affected as patients may forget a dose or become confused and skip a one [60].

An additional decision criterion is the mechanism of action (serotoninergic, norepinephrinergic, dopaminergic). Interestingly, the mechanism of action does not appear to be a major component influencing the choice of antidepressants [61, 62] possibly due to a lack of association with efficacy and effectiveness of the drug, a hypothesized overlap in final pathways, (e.g. the restoration of regulation of stress hormones, the changing of the monoaminergic neurotransmission) and an apparent interchangability between drug combinations [63, 64]. The mechanism of action might play a more prominent role in drug selection in the future, as novel antidepressants enter the market. Agomelatine is an example of a drug with melatonergic agonist properties [65]. Therefore, this is the first antidepressant drug whose major mechanism of action is not the influence on monoaminergic neurotransmission. On the other hand, it also works due to an antagonistic property at the serotonergic system.

Current Canadian guidelines [66, 67] – just to mention one example – state that SSRIs, serotonin and noradrenaline reuptake inhibitors SNRIs, and other newer agents are first-line medications because they have better safety and tolerability profiles than older medications like TCAs and MAOIs. These first-, second- and third-line antidepressants, their mechanism of action and dosage according to the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines can be found in Table **3**. This table provides an overview of worldwide available antidepressants even if they are not available in Canada.

TCAs are recommended as second-line antidepressants in these guidelines because of tolerability and safety issues and MAOIs are recommended as third-line because of tolerability and safety issues and dietary and drug restrictions. Trazodone is also considered a second-line antidepressant because it is very sedating at therapeutic doses. The selective MAO-B inhibitor, selegiline transdermal, has a better tolerability profile than the older MAOIs but because both dietary (at doses higher than 6 mg) and drug restrictions are required, it is recommended as a second-line antidepressant.

Although the evidence for these guidelines is limited to published reports, there are numerous published abstracts of RCTs demonstrating efficacy of the atypical antipsychotic, quetiapine XR, as monotherapy for unipolar, non-psychotic major depressive disorder [67, 68]. Given the strength of evidence, quetiapine was included into these guidelines as an efficacious antidepressant, although it belongs to the class of antipsychotics. However, given its tolerability profile and relative lack of comparative data with SSRIs and newer agents, quetiapine XR is recommended as a second-line antidepressant [67].

3.2.3. Patient Characteristics

Patient characteristics that influence the choice of antidepressant can be classified into the following sub-categories: history of medication use, patient demographics (age, race, ethnicity), socioeconomic status (insurance coverage and income), perceptions and attitudes of the patient and their family, co-morbidities, pregnancy, and breast feeding.

First, medications used in the past by the patient or her/his family member are often selected for current use, provided that they were successful. This is common in practice, although it is based on clinical experience and not on scientific evidence [60]. We already reported the possibility that the selection of subsequent treatments may be affected by the success or failure of past treatments in the "illness characteristics" section.

Second, a patient's demographic profile plays a role in the selection of a drug. Age must be factored into the decision, specifically in the case of children and adolescents and senior patients [52, 69], as well as for women of reproductive age who might get pregnant [70, 71]. Race and ethnicity influence the drug selection [20]. In general, the rates of antidepressant use among racial or ethnic minorities are low [72] for two possible reasons. Disadvantaged groups such as African Americans are less likely to be appropriately diagnosed and treated [73]. African Americans and Hispanics are less likely than Whites to find antidepressant medication acceptable, and favour counselling. Clinicians must consider patients' cultural and social contexts when negotiating treatment decisions for depression [74].

Third, the patient socioeconomic status might be a driver of drug choice. Low income patients who do not have insurance coverage are likely to prefer less costly drugs, independently of other criteria for drug choice [61]. Table **4** provides an overview of antidepressant costs comparison in the US. In the US, some drugs are available for a low monthly cost through programs offered by large chain stores. For example, Kroger, Sam's Club, Target, and Walmart offer a month's supply of selected generic drugs for $4 or a three-month supply for $10. Other chain stores, such as Costco, CVS, Kmart, and Walgreens, offer similar programs. Some pro-

Table 3. Summary Information for Antidepressants: Level of Recommendation, Mechanism of Action and Dose Range. Table Adopted from [67]

Antidepressant	Mechanism	Dose Range
First-line recommendations		
Agomelatine [Valdoxan]	MT1 and MT2 agonist; 5-HT2 antagonist	25–50 mg
Bupropion [Wellbutrin]	NDRI	150–300 mg
Citalopram [Celexa, Cipramil]	SSRI	20–60 mg
Desvenlafaxine [Pristiq]	SNRI	50–100 mg
Duloxetine [Cymbalta]	SNRI	60–120 mg
Escitalopram [Cipralex, Lexapro]	ASRI	10–20 mg
Fluoxetine [Prozac]	SSRI	20–80 mg
Fluvoxamine [Luvox]	SSRI	100–300 mg
Mianserin [Tolvon]	α2-adrenergic agonist; 5-HT2 antagonist	60–120 mg
Milnacipran [Ixel]	SNRI	100–200 mg
Mirtazapine [Remeron]	α2-adrenergic agonist; 5-HT2 antagonist	30–60 mg
Moclobemide [Manerix]	Reversible inhibitor of MAO-A	300–600 mg
Paroxetine [Paxil]	SSRI	20–60 mg; 25–50 mg for CR version
Reboxetine [Edronax]	Noradrenaline reuptake inhibitor	8–12 mg
Sertraline [Zoloft]	SSRI	50–200 mg
Tianeptine [Stablon, Coaxil]	Serotonin reuptake enhancer	25–50 mg
Venlafaxine [Effexor]	SNRI	75–375 mg
Second-line recommendations		
Amitriptyline, clomipramine and others	TCA	Various
Quetiapine [Seroquel]	Atypical antipsychotic	150–300 mg
Selegiline transdermal [Emsam]	Irreversible MAO-B inhibitor	6–12 mg daily transdermal
Trazodone [Desyrel]	Serotonin reuptake inhibitor; 5-HT2 antagonist	150–300 mg
Third-line recommendations		
Phenelzine [Nardil]	Irreversible MAO inhibitor	45–90 mg
Tranylcypromine [Parnate]	Irreversible MAO inhibitor	30–60 mg

Abbreviations: 5-HT=5-hydroxytryptamine (serotonin); ASRI=allosteric serotonin reuptake inhibitor; MAO=monoamine oxidase;MT=melatonin; NDRI=noradrenaline and dopamine reuptake inhibitor; SNRI=serotonin and noradrenaline reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

grams have restrictions or membership fees, so doctors and patients could check the details for restrictions and make sure the drug is covered [9]. For further details regarding costs of antidepressant therapy see section "pharmacoeconomics".

Fourth, patient preferences should be taken into account and additional information regarding action, efficacy, drug interactions and side effects of these alternative therapies should be given and alternatives should be discussed before making a shared decision [38, 75-78]. Patients and their families often have strong opinions about the use of antidepressants as compared to alternative therapies such as omega-3 fatty acids, St. John's Wort (SJW), folate, S-adenosyl-l-methinine, acupuncture, light therapy, exercise, and mindfulness psychotherapies. SJW, for instance, has been used for centuries to treat a variety of medical illnesses. In Europe, SJW has been a commonly prescribed treatment for depression. Because of potential drug interactions, SJW is not scientifically considered a benign treatment [79]. Patients who choose SJW often have a history of alternative medicine use and a belief in the need for personal control of health. They consider herbal remedies as safe, and they are aware of the ease of use and popularity of SJW [80]. Often SJW users do not inform their primary care providers that they are taking the herb despite the potential drug interactions [79]. Patients' use of all prescribed and over-the-counter medications, herbal remedies, and alcohol and recreational drugs must be accounted for in the selection of antidepressants.

Fifth, co-morbidities and medications used to treat them must be considered in the selection of antidepressants. Both are common among depressed patients. Common co-morbidities of depression are stroke, cancer, Parkinson's disease, substance abuse disorders, coronary heart disease, hepatitis C, anxiety and dementia [81-85].

The analysis of co-morbidities is important in the choice of antidepressants due to potential drug-drug interaction, illness-drug interactions, and potential beneficial effects of specific antidepressants on other illnesses. In terms of drug-drug interactions, treatment of hepatitis C with interferons, for instance, may lead to problems regarding the SSRI degradation within the liver [86]. In terms of the drug-illness interactions, it is common to use antidepressant medications to treat non-depression problems. For instance, anticholinergic TCAs are often prescribed to treat sleeping problems, but can results in a worsening of cognitive and mnestic symptoms in patients with dementia. In the latter case, SSRIs are preferred [87]. Another example of using antidepressants to treat non-depressive symptoms is the use of amitriptiline for migraine prophylaxis, interstitial cystitis, or pain syndromes [88-90]. If depressed patients suffer from these disorders, amitriptiline may be considered as antidepressant to treat both conditions.

During pregnancy, antidepressant treatment might lead to a neonatal withdrawal syndrome, primary pulmonary hypertension [91], other teratogenic effects or an abortion [70]. Additionally, the postpartum and lactation time is crucial as the antidepressant might be transferred into breast milk [92-101], and breastfeeding patients who use antidepressants can experience more severe symptoms, greater functional impairment, more extensive psychiatric histories, and lower quality relationships [102].

3.2.4. Physician Characteristics

Patients with depression are mainly treated by general practitioners (GPs) or primary care practitioners (PCPs), psychiatrists and psychotherapists. Epidemiologic findings indicate that 10% to 15% of primary care patients suffer from depression [103] with most depressed patients presenting to GPs with somatic symptoms of depression or help-seeking behaviors related to physical concerns [103]. Thus, PCPs are ideally positioned to decrease the morbidity, mortality, and cost of depressive disorders by accurate diagnosis and effective treatment of the disorder [104].

Unfortunately, GPs and PCPs do not receive sufficient nor consistent education about depression in medical school, but do receive promotional information from pharmaceutical firms. This form of knowledge transfer does not allow for a solid understanding of pharmacological and psychotherapeutic treatment options [42]. As a result, the appropriateness of treatment is compromised, and potentially further decreased through direct to consumer advertising. The effects of the latter on treatment choice have not been investigated in the literature [20, 105].

Reported or assumed factors that influence the prescribing of antidepressants include: the physician's experience [61], the opportunity for interdisciplinary communication [106], knowledge about how to prescribe an antidepressant to older patients [107], cautiousness in prescribing [108], personal estimations regarding the therapeutical effect of antidepressants [109, 110], the substitutability or complementarity of antidepressants and psychotherapy [111], the physician's concern about the tolerability and safety of prescribed medication [59] or whether the medication increases suicide risk [112], limited time, the physician's own interests, background, and training [113], the physician's conceptualization of depression [107], and the physician's view of their patients [111, 114].

Physicians who conceptualize depression as a biological disorder are more likely to treat with antidepressants, as are those who do not believe patients are not in the position to take part in the decision making process, and that patients in general expect to be treated with medications [10, 111]. Shared decision making between physician and patient adds complexity to the drug selection process by emphasizing patient preferences and practice setting [114].

The patients as well as the physicians belong to the same society in which also philosophical and social opinions and neuroethical viewpoints [115] are prevalent and influence decisions in therapy but also in decisions of health care providers. Some society members think that depressive states are important for spirituality [116]. According to this point of view, treatment with antidepressants leads to loss of self-respect, and one argument against antidepressants is that these drugs lead people in some cases to expect less of themselves and their lives than they ought to [116]. Philosophers articulated the concern that overuse of antidepressants, like any technology, can result in an excessively instrumental approach to life in which there is no rest from incessant manipulation of self and environment. The feared consequence would be the so-called "slavish self," which is pressured by society's unending demand for active productivity to take antidepressants [116]. It has also been discussed that people in developed nations are becoming increasingly intolerant to discomforts that in the past were viewed as routine and that the high rates of antidepressant prescription reflect the denial of a meaning of the suffering [116].

3.2.5. Treatment Setting Characteristics

The treatment setting refers to drug administration in the inpatient or outpatient setting, technical equipment required, and other resource and structural characteristics. The treatment setting further contributes to the selection of antidepressants [75].

Differences in the treatment setting influencing antidepressant treatment decision arise due to the number of patients that present for treatment per time period [117], the differences in symptoms of inpatient and outpatient settings [118], the technical facilities such as therapeutic drug monitoring (TDM) facilities [119], practice arrangements, and/or the availability of alternative treatment options. The precise relationship between the treatment setting types and the particular drugs selected has not been studied explicitly.

Alternative treatments include options such as the already mentioned antipsychotic quetiapine [67], cognitive behavioural therapy [23], electroconvulsive therapy (ECT) [120], or transcranial magnetic stimulation (TMS) [121]. It is not clear how the availability of alternatives affects the discrimination between drugs. Practice arrangements in individual clinics and delivery systems between clinics favour the delivery of health care for acute conditions. The delivery of care for chronic conditions, which requires the building of long term patient-provider relationships, the involvement of patients in clinical decision making, and the networking with specialists are not supported by standard arrangements [113].

The literature also reveals data on the nursing home setting [122], where the size of the nursing home, and related features appear to be associated with the use of antidepressants in general, although not the choice of any particular antidepressant. The use of antidepressants appears to be at least in part financially motivated. Antidepressants are used more often in nursing homes with a higher percentage of privately funded patients, more professional nursing staff, and smaller facilities. Use of antidepressants is lower in for profit facilities, and those employing full time physicians [123].

3.2.6. Decision Supports

Decision supports include biomarkers to customize therapies for patients, computational decision aids, and standardization of treatments. These may support the choice of drug, although not facilitate the selection of the most appropriate treatment for individual patients.

Biomarkers to Support Individualized Therapy

Increasingly, pharmacogenetic testing is being advocated as a method for the selection of antidepressants. Currently, the state of clinical evidence has not yet reached a level, where such practice can be supported. It has, however, been suggested that genetic test-

ing as a means to matching the most appropriate antidepressant may lead to a greater number of patients experiencing remission early in treatment [124-128]. For example, Binder *et al*. reported significant associations of response to antidepressants and the recurrence of depressive episodes with single-nucleotide polymorphisms in FKBP5, a glucocorticoid receptor-regulating cochaperone of heat shock protein (hsp)-90 [129]. And Uhr *et al*. reported that polymorphisms in the ABCB1 gene, which regulates the blood-brain barrier, predicted the response to antidepressant treatment in those depressed patients receiving drugs that had been identified as substrates of ABCB1 [130].

Examples of biological predictors that might be relevant to the choice of antidepressants are: metabolites from central nervous system transmitters, the activity of enzymes involved in transmitter metabolism such as MAO and the catechol-O-methyltransferase (COMT), enzymes involved in the metabolism of the antidepressants, neuroendocrinological parameters (dexamethasone suppression test and the combined dexamethasone/corticotrophin releasing-hormone (CRH) test, growth hormone (GH) response to clonidine, thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH), prolactin response to fenfluramine, neurophysiological parameters (REM latency, electrodermal activity, EEG resting activity, EEG reaction to antidepressants), volume dependency of the central serotonergic activity and MR changes [131-137]. A concrete example of use in the recent past was the determination of a polymorphism of the serotonin transporter promoter region (5-HTTLPR) [126, 138]. However, these biomarkers have only been shown to be significantly associated with depression or certain treatment parameters in the framework of group statistics, but did not proof to be of clinical value for the individual patient.

Computational Decision Aids

The use of artificial modelling of patient responses to antidepressants has been suggested as a method to the individualization of treatment for patients. The proposal is to apply either (i) mathematical models of artificial neural networks (ANN), or (ii) the computerized documentation and expert system (CDES) to a pool of clinical information derived from case descriptions by senior psychiatrists. Some success of this strategy was demonstrated [139-141], but the superiority of this strategy over treatment as usual was not established [142, 143]. It would be interesting to investigate the prediction of therapy response if information regarding biomarkers would be computerized in addition to the clinical information. But to the best of our knowledge, this approach has not been pursued yet.

Standardization of Treatments

Standardization of treatment creates a situation where all patients who belong to a specific group receive the same treatment. In theory, the group can be defined by a series of characteristics, although in practice group membership is defined by broad disease characteristics. For instance, all patients with unipolar depression would be offered the same antidepressant regardless of subtype, age, or genetic makeup. More narrowly defined groups allow for an improvement in the appropriateness of treatment for individual patients, including the selection of the best antidepressants, and also the avoidance of unnecessary polypharmacy [142, 144]. The use of measurement-based care and treatment algorithms has been advocated as a key to achieving response and remission [145].

Treatment algorithms are designed to optimize appropriateness and implementation of treatment [142]. They require explicit treatment protocols that provide specific therapeutic pathways and decision-making tools at critical decision points throughout the treatment process [142]. The decision making tools are standardized questionnaires [146], assessment tools [147] to measure depressive symptomatology, chart documentation [114], and decision trees [23].

Examples of successful algorithm projects are the Texas Medication Algorithm Project [148], the STAR*D study [7] and the German Algorithm Project [142] and the algorithm used in the Department of Psychiatry and Psychotherapy in the University Hospital of Leipzig which is explained in the last section of this article. The success of treatment algorithms, however, does not constitute sufficient evidence to support the selection of the first line therapy. The STAR*D study used citalopram as first line therapy, but no data are available to assess success if another antidepressant was to be used [64].

3.2.7. Economic Evidence

The economic analysis of pharmaceuticals, often referred to as pharmacoeconomics, focuses on the estimation of the efficiency of specific drugs expressed in terms of a cost-effectiveness (CE) ratio (cost per life year gained or cost per a disease specific unit of outcome) or cost-utility (CU) ratio (cost per quality adjusted life year gained). The estimation of a CE or CU ratio allows for the comparison across a variety of drugs, not all of which lead to similar outcomes. In theory, this approach would allow the decision maker to rank treatments in order of efficiency and allocate funding to the most efficient treatments [149-151]. While there are four methods to the estimation of efficiency, cost-minimization analysis and cost-benefit analysis are not discussed here, as these are nearly never used in health care evaluations. Cost minimization analysis would require that the outcomes of two competing treatment are identical, which in practice is very unlikely. Cost-benefit analysis requires that one monetize the value of the outcome, which in the case of health care is not appropriate.

Economic analyses are used in a number of Western health care systems to support decisions to fund or not to fund specific drugs. A payer (public or private) can proceed in one of two ways. Either a fixed budget is established *ex ante*, and it is spent on the most efficient treatments until it is exhausted; or the payer establishes a threshold CE or CU ratio and funds all treatments with a CE or CU ratio below the threshold. The latter approach requires that the budget be flexible. Examples of central agencies that produce economic analyses in health care are the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom, the Institute for Quality and Economic Efficiency in Health Care (IQWiG) and the Federal Joint Committee in Germany (G-BA) in Germany, the Autorite de Sante (HAS) in France, or the Canadian Agency for Assessment of Drugs and Technologies in Health (CADTH) in Canada.

From the perspective of the physician, a conflict arises in the sense that what is most efficient or best for society as a whole is not necessarily in the best interest of individual patients. Most often clinicians are not put in the position where giving treatment to one patient leaves less treatment for another patient. The physician's task is to select treatments that are best for individual patients, and only when two choices are equal in this regard, can economic analysis play a role.

The use of economic analyses, whether by policy makers or individual physicians, is difficult in practice for two broad reasons: (i) the methodological debates surrounding the analyses, and (ii) the technical nature of the report and associated difficulty of interpretation by non economic audiences [152-157].

A discussion of the methodological debates surrounding CE and CU analyses is beyond the scope of this paper. Suffice to say that there are many, including how to value outcomes (the quality adjusted life year measure has been questioned extensively), how to value costs, how to model a patients disease progression beyond trial data, or how to account for uncertainties. Which perspective is taken on each of these questions affects the results of the economic analysis. Consequently the results are often inconsistent between studies. This makes economic analysis less usable in the selection of treatments. Economic analysis of antidepressants is further com-

plicated by the typical challenges with measurement, and some measurement issues that are unique to their context. Measurement problems arise on the cost and the outcomes side of the analysis. There is not an agreement among analysts, which costs are to be included in the CE or CU estimation. The conceptualization of costs can be as narrow as the cost of drug acquisition. As mentioned before, direct cost of the 12 most commonly prescribed drugs used in different doses and different formulations in the US are shown in Table **4**. But measurement of costs can be expanded from these direct costs to costs of drug administration, laboratory test, management of adverse events, and other health care costs related to an episode of depression, or can be as broad as to include all societal direct and indirect costs including patient and family time, and productivity lost due to the illness [151, 158, 159].

In the context of depression, outcomes can and have been measured using a variety of indicators, such as remission rates, hospitalizations, relapse, or number of successfully treated patients [16, 32, 160, 161]. A success in treatment could be measured using instruments such as the Hamilton Depression Rating Scale (HAMD) [162], the Beck Depression Inventory (BDI) [163] or the Montgomery-Asberg Depression Rating Scale (MADRS) [164]. The variety of outcomes measures and the lack of consensus about the optimal outcomes measure create a problem for economic analysis in terms of comparability between studies. For a CE ratio to be comparable to another, the outcome must be expressed in the same units of measurement. The life years gained measure has been proposed (and used) as the standardized measure of outcome in a CE analysis. This is most feasible when the underlying clinical study uses overall survival as the primary endpoint, but this is rare is clinical studies of depression.

Additional variables that can affect both costs and outcomes of depression therapy include adherence rates, premature discontinuation, concomitant use of anxiolytics or sedative hypnotics, necessary switches in antidepressants [16, 32, 160].

The example of escitalopram illustrates the challenges of interpreting CE and CU analyses in the context of antidepressants. This drug was compared to other SSRIs and to venlafaxine, as first line and as second line therapy, using a variety of analysis types (CE, CU, and meta-analyses thereof), and in a number of jurisdictions, including the United States [165], Denmark [161], the United Kingdom [166, 167], Belgium [168], Austria [32] and New Zealand [41, 169]. Results vary across studies to the point of rendering economic evidence of little use to decision making. Two studies favour escitalopram over venlafaxine [166, 168], one favours venlafaxine [165], and two show equivalence in terms of the cost effectiveness of these two drugs [161, 166]. Escitalopram is also shown non-inferior to venlafaxine [170], superior to sertraline [171], superior to citalopram [166], and superior to fluoxetine [169]. Although the conclusion was to recommend escitalopram as first line therapy in patients with major depressive disorder [32, 169], the non-comparability of results due to the different applied methods undermines this recommendation.

Additionally, one has to assume that in a country with a public health care system such as in the UK or a health system based on statutory health insurances such as Germany, the individual economic or financial possibilities of a patient may not play the same important role for the individual antidepressant decision of a physician and his individual patient compared to a country such as the US, where health insurances are not required for everybody by law. However, on a national economic level, economic evidence is crucial in the publicly funded systems, particularly if they have drug plans. This is because what is funded by the plan directly affects what is available for physicians to prescribe. Therefore, pharmacoeconomic considerations seem to be more relevant in antidepressant decision making either at an individual or at a national economic level depending on the health care system.

To conclude, even if a physician decided to use economic evidence as a decision support tool, the theoretical and practical complexities of economic analyses in health care reduce the feasibility of their use in clinical practice. Studies differ by method of analysis, by measure of outcome, by cost measures, and by comparators. For a physician, who is generally not specialized in economic methods, the interpretation of these studies becomes next to impossible.

4. EXAMPLE OF A CLINICAL APPLICATION

At the University Hospital of Leipzig, Department of Psychiatry and Psychotherapy (Clinical Director: Professor Ulrich Hegerl, MD), patients suffering from a depressive episode without psychotic features are treated according to a therapy algorithm shown in Table **5**, which was developed referring to the German Algorithm Project (GAP; [142]) and consisting of five treatment stages including antidepressant monotherapy, augmentation with lithium, combination of two antidepressants, an irreversible MAOI and electroconvulsive therapy (ECT). This treatment algorithm was established in the department and serves as an inter-office treatment guideline.

Treatment stages are maintained at least for 4 weeks until a decision is made at a critical decision point (CDP) about the maintenance of the current or initiation of the next treatment stage. These decisions are based on the HAMD, 17-item version. HAMD-Scores will be obtained biweekly by the treating psychiatrist. Decision making takes place according to the criteria used in the GAP.

The algorithm starts with the dose escalation or the termination of the antidepressant treatment the patient already received before being referred to our institution. According to the clinician's assessment of this strategy, the patient enters the first treatment step of the algorithm which consists of the antidepressant monotherapy with either escitalopram or mirtazapine. We have chosen these two antidepressant possibilities as they are two of the four most efficacious newer antidepressants [39], and with these two antidepressants we have one sedative and one non-sedative antidepressant as well as one drug leading to weight gain and one drug not leading to weight gain available. Mirtazapine treatment should be avoided in obese patients as first-line antidepressant medication. On the other hand, it is not realistic to treat all depressed patients without the possibility of an application of a sedative antidepressant. Therefore, mirtazapine should be a treatment option despite its property to induce weight gain. In the near future, agomelatine will possibly show adequate antidepressant efficacy compared mirtazapine and may gain the same evidence. In this case, we may apply agomelatine instead of mirtazapine.

The second step is augmentation of the antidepressant with lithium, because this augmentation strategy has still the best evidence [172].

The following third step would be the combination of two antidepressants. The combination of a selective serotonin reuptake inhibitor (SSRI) such as escitalopram with mirtazapine has been shown to be useful and effective in several studies, as these two antidepressants engage separate mechanisms of action [173]. And the last two treatment steps are the irreversible MAOI tranylcypromine or ECT which are still standard therapies for therapy-resistant depression [174, 175]. Prior to the therapy with an irreversible MAO inhibitor, a psychopharmacological therapy break of two weeks is necessary due to possible drug interactions. Attention has to be paid to all indications as well as contra-indications of the mentioned therapeutic strategies. If a medication is not allowed to be given to a patient (for example lithium to a patient with a kidney or thyroid disease), the next applicable treatment steps follow. Similarly, all mandatory physical and laboratory examinations prior and during the treatment with the specific psychopharmacological drugs are performed in the framework of the treatment algorithm.

Table 4. The 12 Most Commonly Prescribed Antidepressants in the US, Their Brand Names, Frequency of Use and Average of monthly Cost According to the Monthly Cost of the Antidepressant Drug [9]

Generic Name and Strength*	Brand Name[A]	Frequency of use [B]	Average monthly cost[C]	
Bupropion 75 mg tablet	Wellbutrin	3/d	$283	
Bupropion 75 mg tablet	Generic	3/d	$53	
Bupropion 100 mg tablet	Wellbutrin	3/d	$360	
Bupropion 100 mg tablet	Generic	3/d	$62	
Bupropion 100 mg SR tablet	Wellbutrin SR	2/d	$254	
Bupropion 100 mg SR tablet	Budeprion SR	2/d	$94	
Bupropion 100 mg SR tablet	Generic	2/d	$74	
Bupropion 150 mg XR tablet	Wellbutrin XL	1/d	$235	
Bupropion 150 mg XR tablet	Budeprion XL	1/d	$131	
Bupropion 150 mg XR tablet	Generic	1/d	$122	
Bupropion 150 mg SR tablet	Wellbutrin SR	2/d	$263	
Bupropion 150 mg SR tablet	Budeprion SR	2/d	$76	
Bupropion 150 mg SR tablet	Generic	2/d	$62	
Bupropion 200 mg SR tablet	Wellbutrin SR	2/d	$499	
Bupropion 200 mg SR tablet	Generic	2/d	$166	
Bupropion 300 mg XR tablet	Wellbutrin XL	1/d	$324	
Bupropion 300 mg XR tablet	Budeprion XL	1/d	$118	
Bupropion 300 mg XR tablet	Generic	1/d	$120	
Bupropion 348 mg XR tablet	Aplenzin	1/d	$228	
Bupropion 522 mg XR tablet	Aplenzin	1/d	$540	
Citalopram 10 mg tablet	Celexa	1/d	$127	
Citalopram 10 mg tablet	Generic	1/d	$33	$
Citalopram 20 mg tablet	Celexa	1/d	$129	
Citalopram 20 mg tablet	Generic	1/d	$31	$
Citalopram 40 mg tablet	Celexa	1/d	$143	
Citalopram 40 mg tablet	Generic	1/d	$38	$
Desvenlafaxine 50 mg SR tablet	Pristiq	1/d	$157	
Desvenlafaxine 100 mg SR tablet	Pristiq	1/d	$157	
Duloxetine 20 mg capsule	Cymbalta	1/d	$166	
Duloxetine 30 mg capsule	Cymbalta	1/d	$181	
Duloxetine 60 mg capsule	Cymbalta	1/d	$181	
Escitalopram 5 mg tablet	Lexapro	1/d	$125	
Escitalopram 10 mg tablet	Lexapro	1/d	$121	
Escitalopram 20 mg tablet	Lexapro	1/d	$124	
Fluoxetine 10 mg capsule	Prozac	1/d	$227	
Fluoxetine 10 mg capsule	Generic	1/d	$22	$

(Table 4) Contd....

Generic Name and Strength*	Brand Name[A]	Frequency of use [B]	Average monthly cost[C]	
Fluoxetine 10 mg tablet	Generic	1/d	$41	$
Fluoxetine 20 mg capsule	Prozac	1/d	$225	
Fluoxetine 20 mg capsule	Generic	1/d	$22	$
Fluoxetine 20 mg tablet	Generic	1/d	$27	
Fluoxetine 40 mg capsule	Prozac	1/d	$449	
Fluoxetine 40 mg capsule$	Generic	1/d	$56	$
Fluoxetine 90 mg DR capsule	Prozac Weekly	1/w	$176	
Fluoxetine 90 mg DR capsule	Generic	1/w	$136	
Fluvoxamine 50 mg tablet	Generic	2/d	$106	
Fluvoxamine 100 mg tablet	Generic	2/d	$99	
Fluvoxamine 100 mg CR capsule	Luvox CR	1/d	$213	
Fluvoxamine 150 mg CR capsule	Luvox CR	1/d	$234	
Mirtazapine 7,5 mg tablet	Generic	1/d	$77	
Mirtazapine 15 mg tablet	Remeron	1/d	$155	
Mirtazapine 15 mg tablet	Generic	1/d	$44	
Mirtazapine 15 mg dissolvable tablet	Remeron	1/d	$131	
Mirtazapine 15 mg dissolvable tablet	Generic	1/d	$67	$
Mirtazapine 30 mg tablet	Remeron	1/d	$162	
Mirtazapine 30 mg tablet	Generic	1/d	$44	
Mirtazapine 30 mg dissolvable tablet	Remeron	1/d	$124	
Mirtazapine 30 mg dissolvable tablet	Generic	1/d	$71	$
Mirtazapine 45 mg tablet	Remeron	1/d	$190	
Mirtazapine 45 mg tablet	Generic	1/d	$49	
Mirtazapine 45 mg dissolvable tablet	Remeron	1/d	$133	
Mirtazapine 45 mg dissolvable tablet	Generic	1/d	$73	
Nefazodone 50 mg tablet [D]	Generic	2/d	$65	
Nefazodone 100 mg tablet [D]	Generic	2/d	$66	
Nefazodone 150 mg tablet [D]	Generic	2/d	$68	
Nefazodone 200 mg tablet [D]	Generic	2/d	$65	
Nefazodone 250 mg tablet [D]	Generic	2/d	$70	
Paroxetine 10 mg tablet	Paxil	1/d	$142	
Paroxetine 10 mg tablet	Pexeva	1/d	$196	
Paroxetine 10 mg tablet	Generic	1/d	$20	$
Paroxetine 20 mg tablet	Paxil	1/d	$143	
Paroxetine 20 mg tablet	Pexeva	1/d	$201	
Paroxetine 20 mg tablet	Generic	1/d	$22	$
Paroxetine 30 mg tablet	Paxil	1/d	$154	

(Table 4) Contd....

Generic Name and Strength*	Brand Name[A]	Frequency of use [B]	Average monthly cost[C]	
Paroxetine 30 mg tablet	Pexeva	1/d	$207	
Paroxetine 30 mg tablet	Generic	1/d	$38	$
Paroxetine 40 mg tablet	Paxil	1/d	$163	
Paroxetine 40 mg tablet	Pexeva	1/d	$214	
Paroxetine 40 mg tablet	Generic$	1/d	$37	$
Paroxetine 12.5 mg SR tablet	Paxil CR	1/d	$130	
Paroxetine 12.5 mg SR tablet	Generic	1/d	$99	
Paroxetine 25 mg CR tablet	Paxil CR	1/d	$143	
Paroxetine 25 mg CR tablet	Generic	1/d	$106	
Paroxetine 37.5 mg CR tablet	Paxil CR	1/d	$144	
Paroxetine 37.5 mg CR tablet	Generic	1/d	$115	
Sertraline 25 mg tablet	Zoloft	1/d	$152	
Sertraline 25 mg tablet	Generic	1/d	$29	$
Sertraline 50 mg tablet	Zoloft	1/d	$146	
Sertraline 50 mg tablet	Generic	1/d	$28	
Sertraline 100 mg tablet	Zoloft	1/d	$146	
Sertraline 100 mg tablet	Generic	1/d	$28	
Venlafaxine 25 mg tablet	Generic	2/d	$96	
Venlafaxine 37.5 mg tablet	Effexor	2/d	$172	
Venlafaxine 37.5 mg tablet	Generic	2/d	$88	
Venlafaxine 50 mg tablet	Generic	2/d	$96	
Venlafaxine 75 mg tablet	Effexor	2/d	$192	
Venlafaxine 75 mg tablet	Generic	2/d	$89	
Venlafaxine 100 mg tablet	Generic	2/d	$99	
Venlafaxine 37.5 mg XR capsule	Effexor XR	1/d	$168	
Venlafaxine 37.5 mg XR tablet	Generic	1/d	$123	
Venlafaxine 75 mg XR capsule	Effexor XR	1/d	$179	
Venlafaxine 75 mg XR tablet	Generic	1/d	$115	
Venlafaxine 150 mg XR capsule	Effexor XR	1/d	$193	
Venlafaxine 150 mg XR tablet	Generic	1/d	$129	

Abbreviations: SR (sustained-release), CR (continuous-release), XR (extended-release); DR (delayed-release); /d (per day); /w (per week); *selected doses are listed due to space limitations; A. "Generic" indicates drug sold by generic name; B. As typically prescribed; C. Prices reflect US nationwide retail average for January 2011, rounded to the nearest dollar. Information derived by Consumer Reports Health Best Buy Drugs from data provided by Wolters Kluwer Pharma Solutions; D.

All decisions are based on HAMD-21 ratings performed bi-weekly by the treating psychiatrist. After 4 weeks of treatment in a respective stage HAMD-21 scores are obtained by the treating physician. According to their magnitude a current treatment is either deemed not effective (non-response, if HAMD reduction<8 and HAMD score>9) and therefore replaced by the next stage of the algorithm or considered effective, for example if remission (HAMD score<9) is reached. In cases of partial response (HAMD reduction≥8 or reduction of>30% and HAMD>9) the treatment will be maintained, and a final decision is delayed until two additional weeks of the current treatment have passed. This decision tree refers to the German Algorithm Project (GAP; [142]). Moreover, patients will be weighted weekly and blood examination will take place in two-week-intervals as long as the algorithm lasts. If the patients experience remission from depression and remission is

Table 5. Therapy algorithm for the treatment of unipolar depression without psychotic features used in the Department of Psychiatry and Psychotherapy (University Hospital of Leipzig, Germany).

Week	Stage	Pharmacological Treatment		Optional additional treatment
0	0	Dose escalation or termination of pre-existing antidepressant medication		**Psychotherapy**: - Cognitive Behavioral Analysis System of Psychotherapy (CBASP) - Client-Centered Psychotherapy - CBT-based group therapy **Biological Therapy**: - Sleep Deprivation - Light-Therapy **Ergotherapy** **Physiotherapy** **Diet-Counselling**
1	1	**Antidepressant monotherapy**: Escitalopram [10-20 mg/d] or mirtazapine [15-60 mg/d]		
2				
3				
4				
5	2	**Augmentation with lithium**: Augmentation of escitalopram or mirtazapine with lithium [plasma concentration: 0,6–0,9 mmol/l]		
6				
7				
8				
9	3	**Antidepressant combination treatment**: Escitalopram [10-20 mg/d] + mirtazapine [15-60 mg/d]		
10				
11				
12				
13	4	**Psychopharmacological therapy break**	**ECT**	
14				
15		**MAO-Inhibitor**: Tranylcypromine [20-60 mg/d]	**Psychopharmacological therapy break**	
16				
17	5		**MAO-Inhibitor**: Tranylcypromine [20-60 mg/d]	
18				
19		**ECT**		
20				

confirmed after two weeks, the patient stays at this medication and its dose according to the generally accepted recommendations.

Optional additional treatment strategies include cognitive behavioural analysis system of psychotherapy (CBASP), client-centered psychotherapy, cognitive behavioural therapy (CBT) based group therapy, sleep deprivation, light therapy, ergotherapy, physiotherapy and diet counselling. As additional medication, melperone (up to 200 mg/day), zopiclone (up to 15 mg/day) or lorazepam (up to 4 mg/day) are allowed.

Although escitalopram demonstrates superior efficacy compared with citalopram [39, 176] and was economically proven as demonstrated above, in February 2011, the Federal Joint Committee in Germany (G-BA) recommended to group escitalopram together with citalopram in a reference price group, indicating a fixed price for reimbursement on escitalopram in Germany. The recommendation was approved by the German Ministry of Health in April 2011.

The approval forced psychiatrists in private practice to prescribe alternative antidepressants. This meant that a patient which recovered in our hospital during escitalopram treatment had to change his antidepressant drug after discharge from the hospital. Therefore, we were forced to suspend the algorithm in order to avoid the change of antidepressants for a patient after discharge from April 2011 onwards. On December 6th 2011, the State Social Security Court of Berlin-Brandenburg preliminarily suspended this decision of the G-BA and the German Ministry of Health. Therefore, it became again possible to prescribe escitalopram without additional payment in a pharmacy for German patients. Due to this judgement of the court, we were able to re-implement our algorithm in December 2011.

This treatment algorithm shows how drug-, patient- and disorder-related factors influence a standardized treatment decision according to an algorithm which has been developed by the treating physicians for their specific inpatient setting and how this algorithm has to be adopted according to new scientific evidence as well as political decisions which are or at least claim to be based on data from pharmacoeconomics.

DISCUSSION

A long list of potential determinants of antidepressant treatment choice has been proposed in the literature, and many have been substantiated by empirical evidence. Our framework classifies these determinants into seven categories, including illness and treatment characteristics, patient and physician characteristics, treatment setting characteristics, decision supports and pharmacoeconomic aspects.

Specifically, the choice of antidepressants has been influenced by treatment properties, such as efficacy and effectiveness, and setting, other favourable effects and adverse effects of the drug, by

patient demographics, co-morbidities and preferences of the patient and his family, by subtype or the severity of depression, by the knowledge, experience and beliefs of the treating physician and their relationship to the patient, and by treatment algorithms and guidelines. The availability of alternative treatments such as psychotherapy, ECT, light therapy and sleep therapy further influences the choice of the drug [119, 76]. The use of economic studies is challenging at the physician level of decision making. Philosophical and moral values as determinants of treatment choice, while speculated to play a large role, remain grossly understudied, although is unquestionable that advances in psychiatry raise philosophical, ethical, social and legal issues in relation to the human person [177]. The patients, the physicians, members of health insurances and economists all have philosophical, social and neuroethical viewpoints [178] which can be assumed to influence their decisions regarding antidepressants. It has, for example been repeatedly shown that being depressed or taking antidepressants influences the self concept of depressed patients [179]. And the concern has been articulated that overuse of antidepressants, like any technology, can result in an excessively instrumental approach to life in which there is no rest from incessant manipulation of self and environment. The idea that all steps of decision making can be based on the strict rules of evidence-based medicine is therefore not realistic when considering antidepressant treatment [42].

Individualised decision making is so complex that the rigorous expectations of evidence-based medicine can hardly be fulfilled. At the moment, psychiatrists are not able to individualise treatment decisions in terms of "the right drug for the right patient" and we do not have enough powerful clinical or biological predictors, which would help to predict treatment response in an individual patient [54]. In the near future, it may be possible to combine computational and biological predictors for individual antidepressant therapy.

In this article we focus on antidepressant medication, but did not take into account psychotherapeutical and complementary and alternative medicine treatments, although they are reported to be effective and widely used [180]. Also the widely used combination of antidepressant and psychotherapy was not considered, although this therapy seems to be efficacious as well as cost effective [181] and associated with a higher improvement rate than drug treatment alone [182]. Neither did we address specific therapeutic situations such as partial response or non-response to the therapy, difficult-to-treat or treatment-resistant depression, the occurrence of side effects or the appearance of a somatic disorder during antidepressant therapy. Furthermore, we have to state that this review is intended to highlight several influencing factors, but does not cast judgement about the relative importance of these factors. Comprehensive empirical and experimental studies are needed to provide this information.

We explored briefly which of these determinants of decision making are addressed in the current Canadian and German treatment guidelines. The Canadian (CANMAT) clinical guidelines for the management of major depressive disorder in adults contain the suggestion that the selection of an antidepressant should be individualized based on clinical factors including symptom profile, comorbidity, tolerability profile, previous response, potential drug–drug interactions, patient preference, and cost [67]. As clinical factors that influence antidepressant selection they mention explicitly patient factors as well as therapeutic factors [67]. The patient factors of the CANMAT guidelines include age and sex, severity of the disease, the diagnostic subtype, comorbid disorders, a possible past response to a specific drug, the sensitivity to side effects and potential of biomarkers. These are determinants which are categorized as disorder- and patient-related factors as well as the decision supports factor in the classification in our review. The therapeutic factors of the CANMAT guidelines encompass efficacy, tolerability, safety, real world effectiveness, potential for drug–drug interactions, simplicity of use, possible discontinuation syndrome, costs and the availability of branded vs. generic formulations. Taken together, the "therapeutic factors" of the CANMAT guidelines comprise the factor "treatment" and "pharmacoeconomics" of our review.

The German guideline for the treatment of unipolar depression is summarized in the "S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression" [12, 183]. This guideline also contains several factors which should lead to a specific and individualized decision regarding antidepressant treatment. In brief, the mentioned factors are tolerability, safety and practicability of an antidepressant, the experience of a patient with an antidepressant in an earlier episode of a depressive disorder and their preferences, their comorbidities, the use of other medications, and the individual experience of the treating physician [12, 183]. In addition, electrocardiography and TDM are mentioned. Therefore, these German guidelines include all factors described in this review with the exception of pharmacoeconomics. This may be due to the fact that the German health system is based on statutory health insurances. Within this system, the G-BA and the German Ministry of Health determine what antidepressant drugs are seen as cost-effective and possible to prescribe.

Overall, one has to state that treatment guidelines, for example the above mentioned Canadian and German guidelines, contain the major components influencing antidepressant treatment decision as they are detected by the literature search performed in the framework of this review, even if details may be missing due to national particularities and circumstances.

Rarely considered in the treatment guidelines are physicians' beliefs and physicians' ethical value; yet these fundamental attitudes may also influence treatment decision [114-116]. Moreover, additional factors can also influence differences in specific recommendations, such as the consensus group's composition, underlying mandates, and cultural attitudes [29]. As already discussed above, one has to keep in mind that personal believes and values of a patient and his doctor do also influence treatment decisions in real life. It should therefore be considered that clinical decision making on the whole is not only evidence- but also value-oriented [54] and that even the guidelines are ultimately based on beliefs regarding for example what degree of knowledge has to be assumed to be evidence-based.

The seven categories of antidepressant treatment decision factors can be divided into three groups. The first group would comprise illness and treatment characteristics. These two are the most objective clinical components of matching drug to illness, and they are the most scientifically evaluated of all factors. Patient and physician characteristics constitute the second group of factors related to the individuals taking part in the dyadic process of psychiatric therapy. And the third group of factors are contextual factors comprising practice setting, decision supports and economic evidence. Therefore, one can construct the hypothesis that clinical, individual and contextual factors are the three major groups of factors influencing antidepressant treatment decision. However, this is only an attempt to categorize these factors which has to be evaluated in future studies.

CONFLICT OF INTEREST

Dr. Himmerich received speaker honoraria from AstraZeneca and Servier, consulting fees from Bristol-Myers Squibb, and chemical substances for study support from AstraZeneca, Novartis and Wyeth. Dr. Wranik reported no financial interests or other potential conflicts of interest.

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