The drugs don't work? antidepressants and the current and future pharmacological management of depression

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Abstract: Depression is a potentially life-threatening disorder affecting millions of people across the globe. It is a huge burden to both the individual and society, costing over £9 billion in 2000 alone: the World Health Organisation (WHO) cited it as the third leading cause of global disability in 2004 (first in the developed world), and project it will be the leading cause by 2030. The serendipitous discovery of antidepressants has revolutionized both our understanding and management of depression: however, their efficacy in the treatment of depression has long been debated and recently been brought very much into the public limelight by a controversial publication by Kirsch, in which the role of placebo response in antidepressant efficacy trials is highlighted. Whilst antidepressants offer benefits in both the short and long term, important problems persist such as intolerability, delayed therapeutic onset, limited efficacy in milder depression and the existence of treatment-resistant depression.

Keywords: antidepressants, depression

Introduction

The International Classification of Diseases 10 [World Health Organization, 1992] characterizes depression by three core symptoms: low mood, anhedonia and low energy levels. Other symptoms include reduced concentration and self-esteem, ideas of self-harm, disturbed sleep and diminished appetite, which must persist for 2 weeks minimum. Variation in symptomatology distinguishes between mild, moderate and severe depression. In regards to management, antidepressants are first-line treatment for moderate and severe depression, whereas 'watchful-waiting', exercise and problem solving are recommended for mild depression [Anderson *et al.* 2008].

The serendipitous discovery that iproniazid and imipramine elevate mood implicated a central role of the monoamine system in depression pathology. Thus, all commercially available antidepressants increase levels of serotonin (5HT), norepinephrine (NE) and/or dopamine (DA) via different therapeutic mechanisms. First-generation antidepressants include tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), however they frequently possess undesirable side-effects, and toxic effects in overdose, limiting their application. Newer-generation antidepressants, including the well-known selective serotonin reuptake inhibitors (SSRIs) are more selective and offer improved safety and tolerability (see Table 1 for a selective review of antidepressants; note, however, that this table does not represent an exhaustive review of the antidepressants currently available [Gelder *et al.* 2006]).

Efficacy of antidepressant: a picture of bliss

Clinical trials provide compelling evidence for antidepressant effectiveness, with thousands of positive trials over the past five decades [Hollon *et al.* 2002]. Randomized controlled trials (RCTs) are the gold-standard methodology for assessing efficacy, in which patients are assigned in a double-blind fashion to a placebo (inert 'sugar pill') or active-drug group.

Meta-analyses of RCTs typically report antidepressants as 20–30% more effective than placebo,

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Table 1. Review of antidepressants: therapeutic mechanism and side-effects.

Antidepressant class	Drug	Therapeutic action	Unwanted pharmacological action	Side effect
Tricyclic antidepressants (TCAs)	Clomipramine, imipramine, amitriptyline, desipramine , trimipramine, nortriptyline, protriptyline, maprotiline, amoxapine, doxepine	Block reuptake transporters for serotonin and norepinephrine, and to a lesser extent dopamine	Muscarinic receptor blockade (anticholinergic)	Dry mouth, tachycardia, blurred vision, glaucoma, constipation, urinary retention. Sexual dysfunction, cognitive impairment
			α_1-Adrenoceptor blockade	Drowsiness, postural hypotension, sexual dysfunction
			Histamine H_1 receptor blockade	Drowsiness, weight gain
Monoamine oxidase inhibitors (MAOIs)	Irreversible: phenelzine, tranylcypromine, isocarboxazid	Irreversible and nonselective inhibition of monoamine oxidase (MOA)	Irreversible blockade of monoamine oxidase	Risk of hypertension from dietary amines – tyramine must be avoided, risk of intracerebral haemorrhage
	Reversible: moclobemide	Reversible and selective inhibition of MOA		
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine paroxetine sertraline fluvoxamine citalopram escitalopram	Selective inhibition of 5HT reuptake transporter	Agonist of $5HT_{2C}$ receptor	Gastrointestinal: reduced appetite, nausea, constipation, dry mouth Central nervous: headache, insomnia, anxiety, fatigue, tremor Other: delayed orgasm, anorgasmia
Norepinephrine and dopamine reuptake inhibitors (NDRIs)	Bupropion	Blockade of NE and DA reuptake transporters		Increased risk of seizures
Dual serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine duloxetine	Blockade of 5HT and NE reuptake transporters		Nausea, dizziness, headache, dry mouth, insomnia, increases in blood pressure
Dual 5HT-2 receptor antagonist/5HT reuptake inhibitors SARIs)	Trazodone	Powerfully blocks serotonin-2 receptors with less potent inhibition of 5HT reuptake	Histamine H_1 receptor blockade	Sedation, cognitive impairment
			α_1-Adrenoceptor blockade	Lowers blood pressure, postural hypotension
				Other: priapism (prolonged erections)
	Nefazodone		Histamine H_1 receptor blockade	Sedating, however less so than Trazodone
Noradrenaline and serotonin specific antidepressant (NASSA)	Mianserin mirtazepine	$5HT_2$ antagonism α_1-Adrenoceptor antagonism	Histamine H_1 receptor blockade	Drowsiness, dry mouth, sedation, weight gain
Noradrenergic reuptake inhibitor (NARI)	Reboxetine	Selective inhibition of NA reuptake	Muscarinic receptor blockade	Dry mouth, constipation, headaches

with higher response rates (50% reduction in Hamilton Depression Rating Scale [HDRS] scores) and improved remission rates (HDRS score of less than 8) [Davis *et al.* 1993; Walsh *et al.* 2002; Arroll *et al.* 2005]. Meta-analyses indicate antidepressant effectiveness varies as a function of symptom severity, with greatest efficacy in severe depression. For example, Khan and colleagues found greater symptom change as baseline HDRS scores increased in patients taking antidepressants, whereas no significant relationship was found with placebo [Khan *et al.* 2002]. Similarly, Fournier and colleagues found the effectiveness of imipramine and paroxetine was markedly superior to placebo in patients with highest levels of depression severity [Fournier *et al.* 2010].

Although there is significant variation in the pharmacodynamics of drug receptor and transporter-binding profiles, at a population level there is little evidence to differentiate the various antidepressants' efficacy, and prescribing is generally based upon tolerability. However, it is well recognized that there is significant individual variation in response to different medications, although the so-called pharmacogenetics of such variation is only poorly understood at this time. Recent meta-analyses, which have attracted attention and criticism in equal measure [Cipriani *et al.* 2009a, 2009b, 2009c], suggest modest superiority of mirtazapine, escitalopram, venlafaxine and sertraline over duloxetine, fluoxetine, paroxetine and reboxetine, and when acceptability and cost are added sertraline emerged with the best profile. The modesty of the superiority and the short-term follow up of many trials analysed must temper these intra-class difference results.

Nevertheless the many positive RCTs and millions of patients benefitting from antidepressants is compelling evidence that antidepressants are effective in depression management. This is complemented by neurobiological evidence implicating the importance of the medication-targeted monoamine system in depression, e.g. decreased 5HT levels in cerebrospinal fluid and reduced $5HT_{1A}$ receptor binding potential using positron emission tomography (PET) in depressed patients [Bhagwagar *et al.* 2004]. Further, decreasing 5HT levels via tryptophan depletion (a 5HT precursor) causes relapse of depressive symptoms in previously depressed individuals [Smith *et al.* 1997].

Antidepressants are not for everyone

However, this picture of bliss flies in the face of the rising prevalence of depression despite dramatic increase in antidepressant use [Hollon *et al.* 2002], although it is also argued that depression has previously been underdiagnosed [Fullerton *et al.* 2011]. Poor compliance may be to blame: it is estimated that as few as 30% of patients take psychotropic medication as prescribed [Weich *et al.* 2007; Bockting *et al.* 2008] potentially due to the presence of adverse effects such as sexual dysfunctions in SSRIs coupled with an absence of noticeable therapeutic effects for several weeks, often dissuade patients from taking the medication optimally if at all. Whilst this means patients remain in an undertreated state, it is not to say that antidepressants are ineffective. Further, early benefits may be masked by the insensitivity of RCTs, since Taylor and colleagues have reported therapeutic benefits during the first week of SSRI treatment [Taylor *et al.* 2006].

An alternative explanation of antidepressant inefficacy is the generally held concept that antidepressants are less useful in mild–moderate depression, which represents the majority of depressed individuals, and certainly the vast majority treated in primary care where pharmacological intervention is often the only available therapy [Zimmerman *et al.* 2002; Kirsch *et al.* 2008]. However, this is not to say they do not have a role, and evidence has emerged indicating sertraline is superior to placebo, and on a par with cognitive behavioural therapy (CBT) in this subgroup of patients, particularly for more chronic mild–moderate depressive disorders [Hegerl *et al.* 2010; Cipriani *et al.* 2011; Stewart *et al.* 2011; Undurraga and Baldessarini, 2012] and depression scales may underestimate medication efficacy in this cohort [Isacsson and Adler, 2012]. Thus, it is not the case that antidepressants should not be prescribed to such patients, rather the risk:benefit ratio and availability of other treatments must be carefully considered beforehand.

However, despite considerable improvements in antidepressants, there are treatment-resistant types of depression, which, by definition, fail to respond to two or more antidepressants. Pharmacological treatment is often by augmentation therapy where a mood stabiliser (such as lithium or lamotrigine) or an antipsychotic (such as olanzapine, quetiapine or risperidone) is added to an existing antidepressant [Carpenter *et al.* 2002; Barbosa *et al.* 2003].

Electroconvulsion therapy offers a valuable alternative treatment, with good evidence for rapid efficacy [Frederikse *et al.* 2006]. Despite polypharmacy, with almost limitless combinations of drugs, individuals persist who are not adequately treated. The STAR*D trial, the largest pragmatic multistep drug trial for such treatment resistance, provides sobering reading on the poor outcomes and lack of response of many people to medication [Rush *et al.* 2003]. Nevertheless whilst failing to give clear guidance or evidence for one treatment or protocol over another in treatment resistance, and despite outcomes less successful than one would hope for, it is clear that continued active, rationalized and individually optimized treatment does work for many.

Arrival of Kirsch: a media frenzy

One particular recent meta-analysis has sparked huge scientific and public controversy by stating that placebo response can explain apparent clinical effectiveness of antidepressants. To assess the impact of publication biases Kirsch and colleagues investigated antidepressant efficacy using published and unpublished Food and Drug Administration (FDA) registration trials [Kirsch *et al*. 2008]. Their main finding was that antidepressants were not clinically significant for mild, moderate and severe depression, with a mean drug–placebo difference of only 1.80 points on the HDRS. Clinical significance was only reached in very severe depression, however it was argued that this was due to decrease in placebo response rather than increase in antidepressant response. It was controversially concluded that significant antidepressant–placebo differences have not been established.

Predictably, given the overwhelming evidence base supporting drug efficacy, the reaction against this paper was strong. McAllister-Williams states that the magnitude of therapeutic difference is the difference between drug and placebo, not absolute response to active drug and thus Kirsch's study in fact supports the idea that antidepressants efficacy increases with depression severity [McAllister-Williams, 2008]. In addition, Matthew and Charney noted only group-level effects were addressed as analyses were based on differences in HDRS score between drug and placebo at the study endpoint [Matthew and Charney, 2009]. Huge variation at the patient level in antidepressant response is overlooked; indeed a patient-level meta-analysis found the magnitude of benefit of antidepressant treatment compared with placebo increased with the severity of depression [Fournier *et al.* 2010].

An interesting study by Fountoulakis and Mollera [Fountoulakis and Möller, 2011] has highlighted some important flaws in the calculations of Kirsch and colleagues' meta-analysis [Kirsch *et al*. 2008]. This recent study re-analysed data used in the meta-analysis and reported the correct drug–placebo difference to be 2.18 or 2.68, as opposed to 1.80 stated in the original study. In addition, Kirsch and colleagues failed to report the change in HAMD score was 3.15 or 3.47 points for venlafaxine and 3.12 or 3.22 for paroxetine, which are both above the National Institute for Clinical Excellence (NICE) threshold. Thus, it appears that reporting of results was selective and calculations were flawed, suggesting Kirsch and colleagues' conclusions were unjustified.

In addition, Kirsch and colleagues' study suggests obtaining positive results against placebo is easy; however, failure of trialled antidepressants indicates this is not the case. MERCK and Co invested huge amounts of money into the drug aprepitant (an antagonist of the neurotransmitter substance P) which failed to show advantages over placebo in phase III testing and was withdrawn. A final interesting point is that if antidepressants are not effective, why do patients respond to one antidepressant but not another? Following Kirsch and colleagues' findings, differential improvement between antidepressants would not be expected.

RCTs: gold standard or lead weight?

Whilst Kirsch's conclusion that antidepressants are not effective may go beyond the data, RCT methodological problems may mean antidepressant efficacy is overstated [Greenberg and Fisher, 1994]. One problem is unblinding, where patients know whether they are receiving antidepressants or placebo due to side-effects of psychoactive drugs. Thus, expectations associated with taking active medication may influence outcome, rather than true therapeutic effect [Toneatto and Sellers, 1992]. To overcome this confound, active placebos have been used which mimic side-effects of antidepressants, e.g. drugs with anticholinergic actions mimic tricyclic antidepressant (TCA) side-effects. Moncrieff and colleagues conducted a meta-analysis of RCTs employing active placebos and found only small differences between antidepressants and active placebos, suggesting antidepressant are not very efficacious [Moncrieff

et al. 2004]. However, Quitkin and colleagues state that placebo response rates were similar to trials using inert placebos and that poor response to antidepressants is due to inadequate doses and short duration, making it difficult to detect any significant differences [Quitkin *et al.* 2000].

Employment of the HDRS is another issue as it contains items nonspecific to depression, e.g. six items relate to sleep. These items are likely to respond to nonspecific sedative effects associated with many antidepressants; thus, improvement in baseline score may reflect nonspecific effects and not necessarily changes in mood. Further, substances such as methylphenidate, benzodiazepines and antipsychotics have antidepressant effects suggesting that improvement is not due to unique actions of antidepressants [Khan *et al.* 2002]. It seems more logical to base clinical usefulness on risk:benefit balance in specific situations by taking into account an individual's history, rather than an arbitrary cut-off using the HDRS.

There are also concerns regarding whether patients in RCTS are representative of the wider depressed population due to stringent inclusion and exclusion criteria. For example, patients with low-severity symptoms, comorbid anxiety or substantial suicidal ideation are excluded from phase III clinical trials. Indeed, Wisniewski and colleagues found only 22.2% of patients were eligible for phase III trials in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project, which employed broad inclusion criteria to obtain a representative sample of depressed outpatients [Wisniewski *et al.* 2009]. Important differences in clinical characteristics were found, with excluded patients being more chronically ill with more previous episodes, and greater social and occupational impairment.

Differences were found in treatment outcome, with eligible patients having better outcomes, with better response and remission rates. Thus, RCTs appear limited to patients with greatest likelihood of demonstrating drug–placebo differences and so may give a more optimistic view of antidepressant effectiveness than what is accurate. However, specific inclusion criteria must be used as new compounds lack sufficient safety data and information regarding effects on comorbid conditions.

These methodological problems make it unclear what small differences between antidepressants and placebo are attributable to: is it genuine therapeutic effect, amplified placebo response or nonspecific pharmacological effects such as sedation? This makes it difficult to assess the true efficacy and risk:benefit balance of antidepressants and raises issues of whether antidepressant prescription is appropriate for patients with milder depression.

Antidepressants: buffers of suicidality?

Teicher and colleagues initially reported increased suicidality, i.e. suicidal thoughts, in depressed patients taking fluoxetine [Teicher *et al.* 1990]. An important FDA meta-analysis reported elevated suicidality risk in 18–24-year-old patients taking SSRIs and issued an expanded black box warning reporting increased risk for this age group [Friedman and Leon, 2007]. However, a cause–effect problem presents itself: is suicidality caused by the underlying disorder or treatment? The FDA study reported the risk of suicidal symptoms in nonpsychiatric individuals receiving antidepressant treatment was lower than that of depressed individuals, suggesting depression plays a key role. This small increase in suicidal ideation in adolescents is thought to be due to 'activation' of patients early in antidepressant treatment before depressive mood lifts, making it more likely for patients to act on pre-existing suicidal impulses.

However, several flaws regarding the initial FDA report that antidepressants increase suicidality have been highlighted. For example, the data used was not collected in a standard format, nor were the trials exclusively patients with depression: generalized anxiety disorder, social phobia and obsessive–compulsive disorder were also examined. In addition, data was not prospectively collected to investigate suicidal attempts and limited narrative information was often only available. As such, classification of adverse events necessarily relied on inferences and often departed from standardized suicide assessment scales for children and adults, which in turn questions the strength of the conclusions reached [Klein, 2006].

It has also been argued that the term 'suicidality' was ill-defined and is a very dubious causal surrogate of completed suicide. Klein stated that suicidality does not validly distinguish between impulsive gestures and a true intent to die and, in addition to weak and possibly confounded evidence from pooled trials, the decision reached

by the FDA to issue a black box warning is questionable as it has generated a huge amount of media awareness which often equates increased suicidality with increased completed suicide [Klein, 2006].

A more recent meta-analysis [Gibbons *et al.* 2012] re-analysing these data sets failed to show an increase in suicide risk in young people on either venlafaxine or fluoxetine, although they showed therapeutic benefit in the treatment of their depression; in working age and older adults there was a decrease in suicidal thoughts and behaviour that was mediated by treatment of depression.

Antidepressants have not been conclusively linked to completed suicide, and indeed may reduce such risk: when the expanded warning was issued, a decrease in SSRI use was coupled with an increase in adolescent suicide rates [Khan *et al.* 2000; Fergusson *et al.* 2005; Gibbons *et al.* 2007]. It is undisputed that the largest suicide risk is untreated depression, as suicidal behaviour is high in depressed adolescents before treatment and each depressive episode is associated with an additional 10% risk of chronicity [Keller *et al.* 1992]. Thus, the substantial advantages of antidepressants over untreated depression and chance of successful recovery appear to outweigh the increased risk of nonfatal self-harm, is compelling evidence for the effectiveness of antidepressants in depression management.

Antidepressant treatment in the long term

Substantial benefits are also apparent with long-term antidepressant treatment. Geddes and colleagues report a 70% reduction in risk of relapse compared with placebo, which persisted up to 36 months after recovery [Geddes *et al.* 2003]. Kupfer and colleagues conducted a 5-year maintenance trial with patients receiving continued imipramine or placebo treatment, or imipramine treatment for 3 years followed by placebo for 2 years [Kupfer *et al.* 1992]. Continued imipramine treatment was highly effective in preventing recurrence, with an 11 times greater risk of recurrence for those not receiving imipramine.

However, high rates of relapse after discontinuing antidepressants does not necessarily imply antidepressants are effective, as depressive-like discontinuation symptoms may be misdiagnosed as relapsing [Moncrieff and Kirsch, 2005]. These symptoms may unblind patients making them more vulnerable to relapse through the so-called 'nocebo' effect, in which negative expectations associated with being taken off medication, can induce physical illness. Critics argue that, as patients still relapse when continuing to take medication, antidepressants do not offer a cure to depression, but instead only modify the risk of depressive relapse. Nonetheless, as currently a curative treatment for depression is not available, antidepressants offer substantial benefits compared with untreated depression.

Why is antidepressant efficacy limited?

Whilst it is clear that antidepressants provide substantial benefits for many in the short and long term, it is also evident that problems persist, such as intolerance, delayed therapeutic onset, limited effectiveness and relapse issues. Why is this?

A potential problem as to why antidepressants have limited efficacy is that they act by increasing monoamine levels, although individuals with depression do not suffer lower levels of these neurotransmitters. There is immediate increase in monoamine levels following antidepressant ingestion; yet a therapeutic delay is common. Therapeutic effects would appear to be modulated by subsequent neurophysiological changes such as differential expression of monoaminergic receptor levels and downstream intracellular effects on metabotropic enzyme cascades and subsequent alterations to nuclear transcription of proteins such as brain-derived neurotrophic factor (BDNF). Fundamentally current medications may be hitting the 'wrong' (or at least an upstream and indirect) target, hindering efficacy.

Indeed other neurotransmitters or neuromodulators have been linked to depression. For example, therapeutic effects have been found by increasing dopamine levels using agomelatine (melatonergic MT_1 and MT_2 agonist and $5HT_{2C}$ antagonist) [Den Boer *et al.* 2005]. Substance P (SP: neurokinin; NK) has also been linked to depression, which is logical seeing that NK_1 receptors are colocalized with 5HT neurons in the dorsal raphe. Electrophysiological studies in mice stirred excitement as SP NK_1 receptor antagonists, such as MK-869, desensitised 5HT autoreceptors within 3 hours. It was thought that this may remove the problem of delayed therapeutic onset [Blier *et al.* 2004], however the problem of delayed therapeutic onset remained perhaps attributable to species

differences [Kramer *et al.* 1998]. Nonetheless, it is clear that factors beyond monoamines contribute to depression, highlighting a clear reason for the limited efficacy of antidepressants.

The future of depression treatment

Pharmacogenetics, how and why an individual responds to a given compound, is a nascent field in pharmacology generally and has offered potential to predict and optimize individual responses to medication.

An example in the pharmacotherapy depression was identification in the STAR*D project of polymorphisms associated with favourable antidepressant response, e.g. a functional polymorphism: 5HTTLPR, of the 5HT transporter gene (5HTT) has a short and long allele. The long allele has been associated with better response to SSRIs, whereas the short allele with poorer response in Whites [Schosser and Kasper, 2009]. This fits in with genetic research from Caspi and colleagues that individuals heterozygous or homozygous for the short allele are more susceptible to depression following stressful events [Caspi *et al.* 2003].

Future work in the pharmacogenetics field has potential for changing depression management through the use of biomarkers and genotypes, which may permit early identification of whether an individual will gain sufficient benefits from antidepressants to justify the risks they entail. However, this is far from being achieved and significant problems are inherent in this field, e.g. differences in ethnicity as in the Asian population the short allele of 5HTTLPR polymorphism is associated with better response [Kim *et al.* 2000]. Circumspection is required at this time, and excitement around early findings has been tempered by a failure to replicate these findings [Leuchter *et al.* 2009].

This individualized approach may help overcome the problem of heterogeneity, as currently the disorder of depression is too broad to serve as a useful construct for treatment development. Depression may not be a unitary disorder, but rather an umbrella construct harvesting multiple disorders with varying biological pathophysiology which each require different treatment.

Further novel targets have been provided by alternative theories of depression aetiology. The neuroendocrine theory implicates hormonal abnormalities in depression due to hyperactivity of the hypothalamic–pituitary axis (HPA) meaning there is insufficient feedback suppression of corticotrophin-releasing factor (CRF) and glucocorticoids. Novel treatments have sought to normalize the HPA via CRF_1, CRF_2 and glucocorticoid antagonists, which reduce depressive symptoms. However, the majority of testing has been in mouse models and mixed results have been reported [Nemeroff and Owens, 2002]. This may be because evidence regarding HPA abnormalities is correlational and only 50% of patients show HPA abnormalities.

The plasticity hypothesis associates depression with reduced hippocampal neurogenesis and neurotrophin levels. A popular alternative explanation for delayed therapeutic onset derives from this hypothesis, in which the time lag is attributed to antidepressants causing altering intracellular enzymes (for example, adenylyl cyclase, cyclic adenosine monophosphate [cAMP] and protein kinase A) which activates expression of the neuroprotective BDNF [Malberg and Duman, 2003; Santarelli *et al.* 2003]. Thus, there has been interest in phosphodiesterases inhibitors (PDE4), which induces BDNF gene expression; however, PDE4 have prodepressive actions in areas such as the nucleus accumbens [Berton and Nestler, 2006].

Conclusion

Antidepressants offer substantial benefits in the short and long term to millions of people suffering from depression. To cast them as ineffective is inaccurate and, whilst Kirsch and colleagues opened our eyes to potential bias and inflation in the literature, the potential for such studies to be sensationalized by the media is merely destructive to both drug companies and patients. A key issue disregarded by critics is the patient's point of view, as if the patient is benefiting from antidepressant treatment does it matter whether this is being achieved via drug or placebo effects? However, it is evident that the ideal antidepressant has not been found as three key problems of intolerance, delayed therapeutic onset and limited efficacy persist. It is imperative that future treatment of depression aims to improve this through focusing on novel targets and adopting a more individualized approach. The reality of contemporary psychiatric practice is that these drugs are used, with effect, on a daily basis by millions: practicing clinicians are aware of the limitations, the side effects,

and the need to holistically contemplate the psychosocial needs of the person in front of them. Guidelines are followed in most instances, but clinical judgement and individual pharmacological tailoring leads, with good outcomes for many.

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