The Journal of Mind-Body Regulation

article

# Sub-Therapeutic Doses in the Treatment of Depression: The Implications of Starting Low and Going Slow

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**Psychiatrists who opt to treat depression with antidepressant medication typically "start low and go slow"—initially prescribing modest doses and then gradually increasing them. General practitioners, moreover, tend to prescribe low, even sub-therapeutic, maintenance doses of antidepressants. Indeed, some patients report clinical improvements even while taking extremely low-dose medication. Several meta-analytic findings suggest a negligible clinical benefit of antidepressants over placebos for the treatment of mild-to-moderate depression; of note, both interventions improve depression ratings compared to no-treatment. Do sub-therapeutic doses of antidepressants provide a treatment prospect for healthcare professionals who wish to use placebo-like treatments for depression? An independent line of research supports the notion of a clinically meaningful difference between antidepressants and placebo but suggests that antidepressants can often achieve this difference at doses much lower than those currently recommended. Could the use of sub-therapeutic doses signal attempts at capturing efficacy at below conventional doses? In this paper, we use results from psychiatrist interviews to explore the vagaries of sub-therapeutic doses and shed light on their role in the armamentarium of the modern clinician.**

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## Introduction

Depression, as currently defined, is ubiquitous; however, treatment of this potentially debilitating condition raises many challenges. More than 12% of the Canadian population will suffer from depression at some point in their lives (Patten et al., 2006), with even higher prevalence rates (> 16%) in the United Kingdom (Bird, 1999) and the United States (Kessler et al., 2005). In the last decade, the efficacy of antidepressant medication—a backbone drug of modern psychiatry (Ioannidis, 2008)—has come under intense scrutiny (Pigott, Leventhal, Alter, & Boren, 2010). Findings from independent meta-analyses suggest that antidepressants and placebos hardly differ in clinical benefit, especially for the treatment of mild-to-moderate depression (Fournier et al., 2010; Khan, Leventhal, Khan, & Brown, 2002; Khan, Redding, & Brown, 2008; Kirsch et al., 2008; Kirsch, Moore, Scoboria, & Nicholls, 2002; Kirsch & Sapirstein, 1998; Rief et al., 2009). The rationale behind the "anti" prefix in *anti*depressant is grounded in the chemical imbalance theory (Moncrieff, 2007)—a controversial view purporting that depression is a consequence of neurotransmitter shortage. The scarcity of scientific evidence supporting the chemical imbalance theory as a comprehensive theory for depression (Ioannidis, 2008; Kirsch, 2009; Ruhé, Mason, & Schene, 2007) raises uncertainty as to the biological nature of depression (Beck & Alford, 2009; Lacasse & Leo, 2005). Nonetheless, clinicians appear comfortable prescribing antidepressants to their depressed patients.

Another controversial account proposes that antidepressants are clinically effective at sub-standard doses (Cohen, 2001b; Furukawa, McGuire, & Barbui, 2002; McCormack, Allan, & Virani, 2011; Zilberman, Gorenstein, & Gentil, 2010). Standard starting dose represents the lowest tested amount that elicits a statistically significant benefit over placebo (Sheiner, Beal, & Sambol, 1989), and anything below this benchmark is conventionally considered sub-therapeutic. The small quantity of active biochemical material in such doses is likely to cause no clinical outcome—homeopathic dilutions being an extreme case. Recent reconsideration of early fluoxetine (Prozac) studies (Cain, 1992; Louie, Lewis, & Lannon, 1993; Wernicke, 1988) supports the idea of "starting low"—as low as one quarter (McCormack, et al., 2011) or even one eighth (Cohen, 2001b) of the recommended initial dose found in the product monograph.

Considering the evidence that placebos replicate the bulk of antidepressant drug effects, fractional dose treatments are likely also exerting their effects through placebo mechanisms. Teasing apart the pharmacological influence of sub-therapeutic dose from non-drug effects reifies the precarious relationship between low-dose and placebo. At a certain dose range, drug concentration

is too low to exert an effect better than placebo. If no such limit exists with antidepressants, we can further contextualize their lack of chemical specificity on depressed mood—a fundamental element of the "antidepressants vs. placebos" conundrum.

In light of the contentious state of research on antidepressant medication, we sought to investigate how academic clinicians with experience in direct patient care treat depression in the clinic. In this integrative synthesis, we position subtherapeutic doses and non-drug effects as vehicles to probing underlying clinical conceptualizations of the pharmacological treatment of depression. Relying on insights gleaned from interviews with psychiatrists associated with Canadian universities, we sketch conceptual challenges and uncover tacit attitudes in the contemporary treatment of depression. Prior to this, we present a review of the current literature on placebo and low-dose treatments for depression.

## Background and the current state of affairs

### Placebo Effects in the Treatment of Depression

Mounting psychological, brain imaging, and clinical trial evidence sheds light on the role of placebos in treating depression (Ankarberg & Falkenström, 2008; Kirsch, 2009; Mayberg et al., 2002). One of the most contentious research results has emerged from a trailblazing trajectory of meta-analytic studies examining placebo-controlled clinical trials of antidepressants (Fournier, et al., 2010; Khan, et al., 2002; Khan, et al., 2008; Kirsch, et al., 2008; Kirsch, et al., 2002; Kirsch & Sapirstein, 1998; Rief, et al., 2009). Such studies independently reported modest benefits of antidepressants over placebos, especially for the treatment of mild-to-moderate depression.

In one of the first meta-analyses (Kirsch & Sapirstein, 1998), the investigators included a no-treatment control group in order to determine the extent to which the response in the placebo group resulted from meaningful placebo effects*,†. Their data demonstrated that taking placebo or an antidepressant improved depression symptom ratings to nearly the same extent; receiving no treatment did very little for depression outcomes.

In order to circumvent publication bias towards positive trials (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008), Kirsch and his colleagues used the US Freedom of Information Act to pool results from both the published and unpublished trials submitted to the US Food and Drug Administration (FDA) (2002). With the unpublished data included, their meta-analysis of the top prescribed antidepressants revealed results with even greater magnitude: placebo pills duplicated 80% of the antidepressant effect. The resultant mean difference on the Hamilton Depression Scale was too minute to constitute clinical significance according to the National Institute for Clinical Excellence (NICE) guidelines (National Institute for Clinical Excellence, 2004)‡.

Depression is a heterogeneous condition, characterized in part by a spectrum of severity (Chen, Eaton, Gallo, & Nestadt, 2000; Weissman et al., 1986). Kirsch and colleagues' 2002 meta-analysis did not consider the potential relationship between initial depression severity and drug versus placebo benefits (Elkin et al., 1989; Wilcox et al., 1992). Subsequent independent meta-analyses (Fournier, et al., 2010; Khan, et al., 2002; Kirsch, et al., 2008) sought out this relationship and found such a link. Importantly, however, the increasing benefit of antidepressants over placebos only reached clinical significance in severely depressed individuals (Fournier, et al., 2010; Kirsch, et al., 2008). Many have suggested that the marginal difference between antidepressant and placebo effectiveness may be at least partly accounted for by patients breaking blind—a frequent occurrence due to the absence of common antidepressant side effects from inert placebo pills (Gaudiano & Herbert, 2004; Kirsch, 2009; Kirsch & Rosadino, 1993; Moncrieff, Wessely, & Hardy, 2004; White, Kando, Park, Waternaux, & Brown, 1992). From the clinical trial research, placebos appear as effective as antidepressants in the treatment of mild-to-moderate depression, but how this information translates to the clinical setting remains uncertain.

### Low-Dose Medication in the Treatment of Depression

A revealing meta-analytic finding from the pooled placebo-controlled antidepressant trials demonstrated that dosage was unrelated to the level of improvement (Kirsch, et al., 2002). In fact, for the majority of the commonly prescribed selective serotonin reuptake inhibitors (SSRIs) (Hemels, Koren, & Einarson, 2002), no dose-response relationship has been clearly established (Bijl et al., 2008; Wood & Gram, 1994). Further, for antidepressants such as fluoxetine, a lower limit of effective dose evades documentation. These findings, or lack thereof, do not lend support to a pharmacological explanation for antidepressant action.

Findings from a recent analysis suggest equivalent fluoxetine efficacy among 40mg, 20mg—the current convention for minimum

* Placebo responses are the outcomes generated in the placebo group of a clinical trial. Improvements in this group can be attributed not only to placebo effects but to a host of non-specific factors including spontaneous remission (e.g., recovery from the common flu), regression towards the mean (the tendency for measurements to revert to average levels), natural history of the disease (e.g., the episodic nature of mood disorders), and external changes in the patient's life.

† Placebo effects are psychobiological changes generated through the clinical encounter that are not attributable to the inherent chemical or physical properties of the intervention. Factors that contribute to placebo effects include the expectations and beliefs of the patient; the conditioned response to a treatment; the patient-practitioner relationship; the attention, attitude and personal characteristics of the caregiver; and the context in which the treatment is given.

‡ Clinical Significance Clinical trials can be selectively designed to produce statistically significant results according to formal conventions ($p < 0.05$) that are trivial in the clinic. For trials assessing depression ratings, a consensus by the National Institute for Clinical Excellence has suggested that at least a 3-point difference is required in the Hamilton Depression 51-point Scale to state a clinically important effect.

effective dose—and 5mg (McCormack, et al., 2011 cf Wood & Gram, 1994). Based on efficacy evidence and with the intent of minimizing costs and harms, the authors recommend starting medications at half or even one-quarter the standard starting dose in several conditions, including depression. They further assert that a very low dose provides a compromise between capturing the placebo effect and providing a legitimate therapy.

Several reviews support the low-dose approach to treatment, claiming that existing guidelines are over-inflated. Cohen reported (2001b, 2004) that, when establishing the dosing recommendations, members of industry and regulatory agencies suppressed or ignored the early low-dose fluoxetine studies (Cain, 1992; Louie, et al., 1993; Wernicke, 1988) and reviews (Salzman, 1990; Schatzberg, 1991; Schatzberg, Dessain, O'Neil, Katz, & Cole, 1987; Stewart, Quitkin, & Klein, 1992; Wood & Gram, 1994). A number of other antidepressants seem to have inflated dosing guidelines—for example, drugs such as buproprion, citalopram, escitalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine—prompting recommendations to start them at doses as low as one eighth of the guidelines appearing in the product monographs (Cohen, 2001a, 2001b, 2004). Striving for the lowest possible therapeutic dose is certainly an admirable clinical virtue; however, we must juxtapose the evidence for low-dose efficacy with the evidence for the placebo component of antidepressant action. The question remains: How do clinicians mobilize this information when rationalizing antidepressant prescriptions and dosing?

### Sub-therapeutic doses in the clinic

In a recent effort to assess the controversial topic of placebos in medical practice, Raz and colleagues surveyed over 600 Canadian physicians about their use of certain treatments in situations without demonstrated or expected benefits (2011). Results revealed that 38% of psychiatrists administer sub-therapeutic doses of medication—a frequency of over six-times that of non-psychiatrists. Interestingly, only 6% of the surveyed psychiatrists both administer sub-therapeutic doses and admit to having used a placebo in routine clinical practice (Raz, et al., 2011). Moreover, only 2% of the 257 psychiatrist respondents deemed placebos of no clinical benefit. These intriguing findings raise several questions that are especially relevant to the antidepressant context.

In primary care, a number of sources suggest that physicians also administer sub-therapeutic doses and more specifically, for the treatment of depression (Beaumont, Baldwin, & Lader, 1996; Gilbody, Sheldon, & Wessely, 2006; Katon, Von Korff, Lin, Bush, & Ormel, 1992). Unlike psychiatrists, however, the evidence of sub-therapeutic dosing in primary care comes from third party assessments of depression treatment in that setting. Critical accounts suggest that primary care physicians are treating depression sub-optimally by prescribing sub-therapeutic doses either unknowingly or out of over-cautiousness. This is supported, at least in part, by the survey finding that psychiatrists admit to using sub-therapeutic doses significantly more than other types of physicians (Raz, et al., 2011).

Establishing a clear consensus for what constitutes a sub-therapeutic dose may elucidate why psychiatrists prescribe them. Perhaps they are using these treatments as "convenient placebos." A very low dose of medication could occupy the middle ground between a pure placebo and a full dose of biochemically active drug. The use of such doses would not require deception; the side effect warnings, the chemical formula, the appearance and the name are all true representations that contribute to the aura and suggestion of taking a drug.

Could prescribing sub-therapeutic doses be a way of acknowledging the aforementioned findings on antidepressants and placebos without venturing into the dubious domain of handing out pure placebos? Alternatively, could the use of such doses signal attempts at capturing insights from the low-dose literature with the aims of achieving therapeutic efficacy at below conventional doses? The present investigation aims to shed light on these questions while unearthing clinical realities of the treatment of depression.

## Methods

We interviewed academic psychiatrists concerning their current conceptualizations of low-dose antidepressants for the treatment of depression. Specifically, we sought motivations for prescribing sub-therapeutic doses of medication.

### Participants

The interviews were conducted on practicing, university affiliated attending psychiatrists in the Toronto and Montreal areas. We targeted these professionals because of their accessibility and expertise. We enlisted the assistance of a senior psychiatrist to recommend experts who would be able to provide a meaningful commentary on the subject matter. Out of 37 psychiatrists whom we contacted, we interviewed all 15 who responded favourably to our request. All participants had experience treating depression. VdJ conducted all interviews.

### The Interviews

Each interview consisted of a semi-structured half-hour interview comprising 13 open-ended questions (see Appendix for the list of questions). The interviewer memorialized the conversations, which were then transcribed for analysis.

### Analysis

We performed a qualitative analysis on the interview results using a modified version of the thematic content analysis method proposed by Burnard (1991). The methodology involved revisiting interview transcripts and notes and identifying salient themes. Next, we reviewed the transcripts to categorize interview responses according to each theme. After thorough analysis of the results with respect to the aims of this study (Strauss, 1987) we rejected the themes that were no longer relevant and collapsed the remaining themes into the following categories:

1) Working definitions of a sub-therapeutic dose of medication.
2) Rationales for prescribing sub-therapeutic doses.
3) Opinions on the placebo effect component of depression treatment.
4) Alterations, communication tactics, and patient conceptualizations of dose levels.

We identified and counted patterns of similar responses within each category. In addition, we highlighted particularly intriguing responses and quotations.

## Results and discussion

### 1) Working definitions of a sub-therapeutic dose of medication.

*Results*. With the exception of one confidant psychiatrist, participants did not seem to have a formal medical definition of sub-therapeutic dose readily available to draw upon. When pressed further, participants came up with one of three broad working definitions for the term. The most common definition (number of participants (N) = 9) was *a dose below the established level of efficacy from the published literature* (e.g., drug monograph reference books, evidence based practice guidelines, systematic reviews or meta-analyses). Another common definition (N = 6), given in addition to the above definition by three participants, was *any dose where no therapeutic benefit can be observed in the individual patient*. Lastly, three participants construed sub-therapeutic as *a dose below the therapeutic level of a drug's primary use but with beneficial effects from its off-label or secondary indications*.

All but two participants indicated caveats to the definitions or provided additional comments in light of the antidepressant context. A major issue was that of inter-individual variability in response to antidepressants—attributed largely to differences in metabolism. Unpredictable outcomes propelled participants to offer a definition of what constitutes a sub-therapeutic dose based on either literature averages with the caveat, "*which may have beneficial effects for some patients*" or based on response in individual patients, adhering to the literal nature of the term. Seven participants highlighted the difficulties in predicting patient sensitivity to a new prescription. However, two participants mentioned that they can approximate the sensitivity of a patient to a new drug based on drug history since patterns of similar responses often exist between drug classes. Regardless of being able to predict sensitivity, almost all participants (N = 13) reported that they occasionally see unexpected improvement to doses of antidepressants that are below established levels of therapeutic efficacy.

When questions concerning the limits of a sub-therapeutic dose arose, it became apparent that its lower limit is, as yet, undefined. In particular, participants were unable to provide clear responses to how one could distinguish between a sub-therapeutic dose, a homeopathic remedy, and a placebo. Similarly, they were largely unable to define what, if any, is the range of sub-therapeutic 'efficacy'. However, three participants did provide reasons for our limited knowledge in that only a sub-set of doses are clinically tested and appear in the published literature, and an even smaller sub-set are commercially available.

*Discussion*. For the purposes of this discussion and for the remainder of the interview, we use the term "sub-therapeutic" in reference to a dose below the minimal effective dose stated in each drug's product monograph. Formally defined, a sub-therapeutic dose means "below the dosage levels used to treat diseases" (*Sub-therapeutic*, 2000) or "indicating a dosage less than the amount required for a therapeutic effect " (*Subtherapeutic*, 2011). The complex patient variability in responses to antidepressant medication, however, seems to complicate these definitions.

The drug literature determines threshold doses by averaging individual responses; a dose exerting no therapeutic effect for the majority of patients, however, may be therapeutically active for others. Environmental, pathophysiological and genetic factors contribute to the inter-individual variability in drug response. Variation in the efficacy of drug metabolizing enzymes is a key differentiating factor (Meyer & Zanger, 1997).

Five to ten percent of the Caucasian population have genetic polymorphisms in the cytochrome P450 enzyme, CYP2D6, that render them poor metabolizers of several commonly prescribed antidepressants (Sachse, Brockmöller, Bauer, & Roots, 1997). However, uncertainty lingers as to how and whether these phenomena wield clinical effects (Bijl, et al., 2008). When it comes to depression *outcomes*, the data have yet to substantiate a clear influence of the most frequent CYP2D6 polymorphisms on clinical responses to antidepressants, especially SSRIs. As such, genetic screening to optimize treatment outcomes remains elusive (Bijl et al., 2008) and serum drug level testing is rare. Although a few participants mentioned drug response history as a helpful guide to antidepressant sensitivity, systematically, the clinician does not know how much of the active compound is reaching a patient's brain. It does not appear that patient variability is easily accounted for by metabolism alone and the clinician has little way of delineating the cause of an unexpected drug response. Further, even the use of sophisticated genetic tools does not seem to provide any clearer answers.

Only three participants gave voice to limitations in understanding lower limits of effective dose based in practical issues that resonate with those of the low-dose literature (Cohen, 2001a, 2001b, 2004; McCormack, et al., 2011). Although inflated dosing guidelines may obscure a clear conceptualization between a sub-therapeutic and a conventional dose of antidepressant, most participants highlighted individual variability instead. Moreover, the general inability of participants to define a limit between a sub-therapeutic dose and a placebo may suggest a broader conceptual grey zone extending from conventional dose entirely to placebo.

### 2) Rationales for prescribing sub-therapeutic doses.

*Results*. The majority of participant psychiatrists stated that administering sub-therapeutic doses of medication did not equate to giving a placebo. This sentiment was well-summarized by one participant who said, "If [a sub-therapeutic dose] were the same as a placebo, then you could give just about anything." By partial exception, one participant asserted: the only utility for a sub-therapeutic dose of drug intended for its primary indication would be for the placebo effect. He added that he would never prescribe medication with this rationale.

Since it did not seem that participants could be prescribing sub-therapeutic doses for their placebo-like qualities, we questioned what other rationales they may have. The situations in which participants recalled prescribing sub-therapeutic doses of antidepressants were mostly when initiating the "start low, go slow" titration technique. Four of the participants that reported using this technique added that they usually start with the minimum therapeutic dose instead of a sub-therapeutic one, especially in the adult population. Two-thirds of participants emphasized tolerance building and minimizing side effects as the rationale for slowly increasing the dose from a low level. Three participants stated that starting at lower doses can also provide a level of comfort or allay anxiety. One participant reported this reason as a primary rationale for starting at such doses. Striving for the lowest effective dose, regardless if it were below conventional levels, was the rationale for starting low between two participants. With the exception of these two, the consensus among participants was that they do not expect any clinical benefit until the patient reaches the established therapeutic dose range.

Since most participants reported that they had seen unexpected responses to sub-therapeutic doses, we sought potential explanations. Nine of the participants arrogated sub-therapeutic dose responses in physiological terms: the patient must "lie on the lower end of the response curve," or be "sensitive to the medication," or "a poor metabolizer." Six participants acknowledged that the response could be due to placebo effects but with no easy way of uncoupling them from the other factors at play. Two participants belittled the need to pinpoint the cause of a satisfactory therapeutic response, especially through costly genetic testing. One participant, however, articulated that readily available genetic testing would be beneficial in certain cases.

Participants also brought up the issue of the exact psychophysical target of antidepressants. Substantial therapeutic benefits can occur from a dose of antidepressant that is sub-therapeutic for managing depressed mood and negative cognitive symptoms, but may relieve certain symptoms, sometimes to the extent that the patient's condition is much improved. Three participants acknowledged that the sedative side effects of certain antidepressants can help depressed patients struggling with insomnia get some much-needed rest. One of them explained that sometimes all a patient needs is a few good nights of sleep to make a significant difference in his or her life. A similar conception was the ability of antidepressants to "take some of the edge off" or produce a "halo effect" in relieving sub-clinical anxiety often comorbid with depression.

*Discussion*. Most people construe placebos as inert. A more nuanced approach, however, includes treatments that are inert for the specific condition but that may otherwise contain active substances (Raz, et al., 2011). Examples of this type of placebo include antibiotics for viral infections, vitamins for the common cold, herbal preparations lacking demonstrated efficacy, and, arguably, sub-therapeutic medications. The opinion among participants that placebos are not equivalent to sub-therapeutic doses parallels recent findings suggesting that the majority of psychiatrists who have administered sub-therapeutic doses in situations of no expected or demonstrated clinical efficacy claim to have never used a placebo in clinical care (84%) (Raz, et al., 2011).

Participants revealed various treatment nuances through their comments on prescribing sub-therapeutic doses. It would seem that participants distinguished sub-therapeutic doses from placebo in terms of intention: although placebo effects may be responsible for the improvement of some patients on a minimal dose, this was not the intended mechanism of action. The intention of most participants starting antidepressant prescriptions low, moreover, was not to capitalize on findings of low-dose efficacy

Rationales for prescribing sub-therapeutic doses seem grounded more in reducing side effects than in enhancing non-drug effects, neither of which follow the classic drug-target convention akin to biomedical pharmacology. Select psychiatrists did demonstrate a certain level of tact in their off-label and psychologically grounded uses of low-dose antidepressants—many of which require tacit clinical knowledge beyond that which can be gleaned from the available evidence base. However, the existing evidence on low-dose efficacy and the substantial placebo component of antidepressant treatment does not appear to have exerted an influence on prescribing practices among the participant psychiatrists.

### 3) Opinions on the placebo effect component of depression treatment.

*Results*. Placebo effects in the treatment of depression were common knowledge among participant psychiatrists. They did not comfortably attribute sub-therapeutic dose improvement solely to placebo effects, however, as they often conceived placebo effects as transitory and outlasted by pharmacological effects. Even with improvement on a sub-therapeutic dose, three participants mentioned that they would increase the dose to the minimum established therapeutic level. Nonetheless, all participants highlighted the importance of additional factors involved in the clinical encounter that are not specific to the treatment modality.

Participants consistently stressed the importance of patient choice and willingness to use pharmacological treatments. All participants said they strongly attend to patient attitudes towards using medications. Participants reported that many patients are wary of taking medication for psychiatric disease. Such reluctance, some suggested, may reflect patient concerns rooted in stigmatization and acceptance of mental illness; other patients fear side effects or ineffectiveness of the medication. On the one hand, two participants emphasized that the treatment effects are likely to diminish if a patient does not believe in the treatment modality. One of these participants often explains this sentiment to patients: "If you think it is going to work, it is probably going to have a different effect than if you take it reluctantly. It is important to talk about whether you think I am shoving this down your throat, or if you actually believe in it." He elaborated: "Even the strongest doses of medications will have little chance of producing satisfactory outcomes if the patient is not convinced that they will work." The other participant reported taking pride in being able to convince patients that the treatment recommendation is a favourable option. On the other hand, many participants cautioned against over-inflating the efficacy of drug treatments to their patients to ensure realistic goals.

According to participants, a sub-group of patients seek out drug treatment or rely heavily on notions of using medications to "fix" chemical imbalances. Pamphlets adorning the participants' waiting rooms clearly communicate this explanation to patients. One such pamphlet ("made possible by an unconditional grant from Wyeth Canada") writes:

> Depression is often described as a "chemical imbalance" in the brain. What this means is that certain neurotransmitters (your brain chemicals) are not at the levels they should be to maintain a positive mood . . . The most common treatment for depression involves medication designed to increase the levels of these neurotransmitters and thus, improve your mood (Mood Disorders Society of Canada, 2009).

Participants rarely broached the subject of antidepressant neurochemical mechanisms. The only two such iterations were: an explanation of how SSRIs can produce an instant "serotonin kick" in the brain but not always treat the target,

and a mechanistic explanation that was cut-short due to the participant's perception that the interviewer (a researcher) may be more of an expert in this area.

Two participants reported that anecdotally based notions of drug treatment can influence outcomes through belief effects. Based on personal accounts from family and friends, patients can arrive at their first appointment with stubborn ideas of what will or will not work, sometimes with a specific drug already in mind. According to these participants, prescribing in-line with patient requests can lead to a type of placebo effect.

*Discussion*. The strongly held notion that placebo effects are only transitory—although findings refute this assumption (Khan, et al., 2008) —seems to create reluctance in attributing antidepressant responses to such effects alone. Our findings suggest that psychiatrists utilize placebo effects in more subtle ways in order to enhance the effectiveness of drug treatment. Engaging in patient belief systems to recruit conviction in the treatment seems critical to maximizing therapeutic outcomes; at least one empirical study would support this notion in terms of improving adherence to antidepressants (Aikens, Nease, Nau, Klinkman, & Schwenk, 2005).

Participants who emphasized the importance of mobilizing patients' anecdotally based perceptions in medications demonstrated the integration of belief effects—independent of biochemical effects—into prescribing practices. Neurochemical based beliefs in depression treatment, borne out of the popular chemical imbalance theory of depression, are likely ingrained in many patients (Leo & Lacasse, 2008); however, from the interviews, it is not clear whether or not psychiatrists have rejected the theory. It is possible that, despite uncertainty in the field, psychiatrists perpetuate this theory, at least indirectly, as a simple explanation for the proposed drug treatment

Whether communicated subtly or overtly, accurately or imprecisely, the meaning imbued in the ability of a drug to fix ills of the mind is certainly a powerful therapeutic ally. In a return to the discussion of dose, interview results demonstrated another way psychiatrists expound this clinical technique of harnessing patient belief and guiding meaning making.

### 4) Alterations, communication tactics and patient conceptualizations of dose levels.

*Results*. Participants suggested that the majority of patients do not understand that different drug potencies relate to different doses. For example, an average 20mg dose of fluoxetine seems much less potent than 125mg of buproprion—a below average dose of this antidepressant. Transparency is necessary, participants contended, but they must take a nuanced approach. For instance, one participant explained, if a patient thinks he is taking a very high dose, he may feel that his illness is more severe and be less likely to recover. Alternatively, if a patient understands his dose as very small, thereby having low expectations of its therapeutic ability, this knowledge can have a nocebo (negative placebo) effect. Two participants therefore prefer leaving dose out of the conversation as much as possible. To avoid the negative influence that dose may have on patients, one participant often emphasizes: "The fact you need a high or low dose has nothing to do with being more or less ill, it is about what your body needs. Some patients need high doses of medication, and that is okay, they may just have a fast metabolism."

In situations where patients are anxious about taking medications, certain participants said they will carefully craft their wording and use phrases such as, "I am putting you on a microscopic dose," "some people take ten times this dose and are just fine" or, "we are still not at the maximum dose level." On occasion, two participants will prescribe a lower dose solely because a patient is hesitant to begin drug treatment. Conversely, participants also depicted patient anxiety about drug weaning. In most instances, psychiatrists will proceed slowly. One participant divulged that for patients who are more anxious and dependent, it is not unusual to maintain them on a dose "that does not make sense for having a pharmacological effect but provides comfort for them." In such cases, the routine of coming to the clinic and receiving the low dose prescription can continue for years.

The majority of participants gave utmost priority to sharing as much information as possible with patients. A few participants commented that elaborating on the scientific underpinnings of their decisions helps the patient understand what to expect from the medication and minimizes non-compliance. For example, when starting a sub-therapeutic dose, participants will explain the tactic of building tolerance to the medication's side effects. Certain participants (N = 6) adopt a more cautionary approach and express to the patient that they do not expect any therapeutic benefits from the starting doses. One participant reported that he will explain to patients that, "if they start to feel the side effects they may be fortunate enough to receive the therapeutic effects; at least the drug is doing something." These participants explained that they are careful not to instill false hopes about the medications, largely

to prevent patient discouragement if the prescription does not work. Two participants went on to say that they rarely promote the placebo effect or use it in their practice.

*Discussion*. Communication is integral to the art of medicine and vital to good physicianship. We typically consider dose, with its exacted milligram quantities of potent ingredients, as a key component of the science of medicine. Through the exploration of dose related questions, it is evident that dose modification represents an interface between the art and science of psychiatric practice. Participants highlighted opportunities to tailor the dose, or the communication of dose, in order to tilt the clinical situation in favour of positive patient expectancies. On occasion, the protocol among participants to equip their patients with as much information as possible may work to the detriment of positive expectations. Considering the evidence in support of placebo effects in the treatment of depression, it is difficult to ascertain how this full-disclosure approach aligns with the complexities of treating depression.

By definition, a sub-therapeutic dose of medication constitutes a placebo-like treatment: it contains active ingredients but at insufficient doses to assume any therapeutic outcomes, individual pharmacokinetic effects notwithstanding. Our findings suggest that the primary rationale for prescribing sub-therapeutic doses of antidepressants is for the patient to build tolerance and minimize adverse events. The clinical stratagem of starting low and going slow, however, can produce surprising therapeutic outcomes at the initial, sub-therapeutic levels. Psychiatrists seem to focus on the role of drug sensitivities in producing such outcomes and admit, albeit hesitantly, that factors other than pharmacology may be equally responsible for these effects.

When presented with positive outcomes, psychiatrists have little incentive to uncover the source of sub-therapeutic drug efficacy. For researchers, on the other hand, the prescription of sub-therapeutic doses of antidepressants provides a unique paradigm for exploring the clinical role of placebo effects without the negative expectancies and ethical issues of pure placebos. The use of sub-therapeutic doses as an alternative to placebos, however, raises its own set of ethical issues surrounding monetary costs, potential harms, patient autonomy and professional form. Under separate cover, we hope to soon provide a comprehensive account of the ethics of sub-therapeutic dosing.

Our investigation of sub-therapeutic dosing practices sheds light on certain clinical realities of using non-drug factors in the pharmacological treatment of depression. Psychiatrists seem to entertain placebo effects in the nuances of psychological manipulations involving dose communication and expectancy-shaping techniques. In certain situations, moreover, dose alterations sustain psychological manipulations, as in the prescription of micro-doses to help allay the anxiety involved in starting or stopping a medication. When it comes to their intentions, however, psychiatrists may shy away from deliberately seeking out placebo effects, even when they are using essentially placebo-like treatments. Nonetheless, placebo effects seem to have at least a candid role in the clinical treatment of depression.

## Limitations and Caveats

The present study constitutes a preliminary investigation of attitudes of practicing psychiatrists toward sub-therapeutic doses in relation to placebo effects in the context of depression. Our main goal was to gauge how psychiatrists conceptualize and integrate these contentious topics in a clinical setting. Although difficult to generalize, the nascent results provide valuable budding insights that will serve to guide further research investigations.

The limited number of interview subjects and the restricted analytical approach hinder our ability to generalize these findings to the wider medical community. Furthermore, the small study sample consisted only of academic psychiatrists (i.e. those working at hospitals and clinics affiliated with a university). This tertiary care setting consists of specialists in psychiatric disorders, but this tier does not handle treatment for the majority of depressive cases. In Canada, as in the United States and the United Kingdom, the bulk of cases fall to the primary care sector (Gilbody, et al., 2006; Goldman, Nielsen, & Champion, 1999; MacMillan, Patterson, & Wathen, 2005; Michalak, 2002). Results from the Mental Health and Well-Being portion of the Canadian Community Health Survey demonstrate that, of the Canadians suffering from the most prevalent mental conditions, 26% consulted a family physician at least once in the 12 months prior to the survey, whereas 12% and 8% consulted a psychiatrist or psychologist respectively (Statistics Canada, 2003). Of those seeking help for depression in the United States, nearly three quarters do so in the primary care setting (Goldman, et al., 1999).

Representation would not be a large issue if depression were treated similarly in the primary and tertiary care settings. When interviewed, some psychiatrists said that their most satisfying

consultations arose from patients referred with "treatment resistant depression" by a primary care physician, only to see clinical benefits with a simple increase in dose. According to those participants who field primary care consults, poor pharmacological treatment outcomes often result from "sloppy" or inadequate dosing. Several sources sustain these claims with reports of suboptimal depression treatment in the primary care setting (Eisenberg, 1992; Gilbody, Whitty, Grimshaw, & Thomas, 2003; Gilbody, et al., 2006; Katon, et al., 1992).

Our results demonstrate the complexities involved in the treatment of depression; however, in order to closely understand the clinical realities, we must cast a wider net and address our questions to a broader audience with further research.

## Conclusions

Exploring the nuances of sub-therapeutic dosing reveals subtleties in clinician behaviours that give merit to the role of placebo effects in the treatment of depression. Psychiatrists are often in the position of interpreting controversial research while exuding the clinical confidence of a caregiver. Converging on the clinically optimal dose requires mastery of the poorly understood dose-response relationship for antidepressants while mediating the influence of individual differences. In addition, clinicians must consider the commonly accepted yet cautiously entrusted role of placebo effects in the recovery from depression. The chemical imbalance theory of depression, although scarcely validated, may play a role in shaping patient and clinician choices and expectations of treatment. The contributions—highlighted here and validated elsewhere—of patient choice (McPherson, 1994), knowledge (Entwistle, Sheldon, Sowden, & Watt, 1998), expectancy (Kirsch, 1999), and belief (Aikens, et al., 2005) to treatment outcomes may benefit from *notions* of specific neurochemical antidepressant action while collectively outperforming *actual* pharmacological action.

The importance of portraying confidence in treatment to the patient (Thomas, 1987) and the perception that placebo effects are only transitory may be factors creating resistance to accepting recent lines of research that cast doubt on the clinical efficacy of antidepressants over placebos. An important consideration is that clinicians do not control for the non-drug effects of their prescriptions by comparing them to placebos. When clinicians observe therapeutic benefits upon an increase in antidepressant dose, we cannot directly attribute this to a biochemical effect since research has demonstrated that placebos elicit a dose-response relationship in depression (Benkert et al., 1997) and in other conditions (De Craen et al., 1999).

Our examination clarifies ambiguities surrounding the use of sub-therapeutic doses of antidepressants for the treatment of depression. Several avenues of inquiry remain, particularly regarding the use of these low doses in primary care and in clinics unaffiliated with academia. We demonstrate that tacit knowledge and carefully crafted tactics are important in steering depressed patients towards recovery—perhaps more so than the ordinances of the existing evidence-based medicine. Relinquishing these roles to general physicians, who currently see a disproportionately large number of depressed patients, creates a needless burden. Psychological, neuroscientific and health directives on depression are abundant but far from comprehensive. Translating research results into meaningful clinical practice should be a primary focus, as prevalence of depression continues to rise worldwide (Mathers & Loncar, 2006). Policy and regulatory directives must concentrate on demanding evidence for lowest minimum effective doses of existing and emerging drug treatments. "The dose makes the difference" (Moore, 1995) and in the antidepressant context, this may mean an arbitrary difference between a drug and a placebo.

## Acknowledgements:

This research was supported by funding from the Canadian Institutes of Health Research (CIHR). We thank Drs. Cory Harris, Elia Abi-Jaoude, Laurence Kirmayer, Adil Virani, James McCormack and Abraham Fuks for their intellectual input on this piece. We also thank the participant psychiatrists who shared their time and thoughts.

## Appendix: Interview Question

Please describe the nature of your practice and your history treating depressed patients.

1) Do you find sub-therapeutic doses clinically useful?

- In what situations and for what types of patients, and types of disorders?

- What do people usually mean by sub-therapeutic on the spectrum from a hair below therapeutic to just above homeopathic? How does this compare to the term "low-dose"?

2) Out of curiosity, how would you define a sub-therapeutic dose if you had to come up with a definition?

- Do you ever see surprising results at a very low dose?

3) If one were to say they have prescribed sub-therapeutic doses, would this equate to saying they have prescribed placebos?

4) How important do you think it is to communicate the dose level at least in qualitative terms to the patient to whom you are prescribing? For example, "I am prescribing you a high dose of the antidepressant fluoxetine." Why or why not?

- Do you see any ulterior psychological effects from the way you communicate dose levels?

5) There are 3 situations where sub-therapeutic doses are admittedly employed: e.g. A patient is transferred from another psychiatrist who already started them on a sub-therapeutic dose. e.g. The start low and go slow dose titration regimen. e.g. Using them as a diagnostic tool, trying to see if they are , patients complaints are not well-grounded, so one gives something very minimal to try and get the complaints to lift

a) Do these situations seem like reasonable utilizations of sub-therapeutic doses?

b) Do you often employ the start low and go slow doing regimen for antidepressant medication?

- Do you often start the regime with a below average dose or an initial starting dose that is known to be therapeutically useful?

6) Presume I came to you depressed, I showed the signs of moderate DSM-4 depression, what would you prescribe for me and in what dose?

7) Do you think adjunct drug therapy to psychotherapy means less of a dose is required than with drug therapy alone?

8) What is your take on Kirsch and colleagues' meta-analyses on antidepressants versus placebos for depression?

9) Why do you think practice guidelines have barely changed in light of the evidence that antidepressants aren't as effective as we thought they were? What factors are creating resistance to accepting this kind of data?

- How do you explain that there is no major up-roar, apart from a temporary wave of media publications (mostly in Europe) while many millions are taking antidepressants and affected by these results?

10) Do you think awareness of the results that cast doubt on the efficacy of antidepressants has in any way altered prescription patterns on an individual physician or psychiatrist level? Or do guidelines normally change before any kind of change in practice takes place?

- What practice guideline do you usually follow for depression? Mix and match? Have you had the chance to read the latest APA guidelines for depression?

11) Do you see clinical trials as an effective means to study psychoactive drug efficacy?

- What is the relative weight of clinical experience in shaping prescription patterns of antidepressants?

12) Do you have any questions or comments for me? Literature suggestions?

13) As a psychiatrist do you think this is a valid line of inquiry, is there something to unravel here? Is this something interesting for psychiatrists?



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