

# A survey of five antidepressant properties influencing clinician's treatment choices in MDD

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**Introduction:** The goal of the present work was to examine how clinicians' perceptions of the properties of antidepressants may influence their choice of antidepressants when treating major depressive disorder (MDD).

**Methods:** 273 of 682 (40%) clinicians attending a psychopharmacology review course responded to a questionnaire designed to explore their practices and perceptions with regards to antidepressant pharmacotherapy.

**Results:** Most clinicians ranked efficacy (57.3%) as the most important factor when selecting antidepressants, followed by safety (23.0%), tolerability (9.4%), rapidity of action (5.2%), and cost (4.9%). However, when presented with hypothetical scenarios in which there was a difference in efficacy between two antidepressant agents, the relative safety, tolerability, and cost of the two agents significantly influenced the likelihood of choosing one antidepressant over another. In fact, clinicians required progressively greater differences in efficacy between two agents in order to select one antidepressant over another given a difference in terms of their safety than tolerability, or their tolerability than cost ( $p < 0.0001$  all comparisons).

**Conclusions:** When selecting an antidepressant, clinicians appear to be most influenced by efficacy, followed by safety. Rapidity of action and cost may be less salient considerations in clinical practice. Further research is necessary to elucidate factors that influence clinicians' choice of antidepressants.

**Keywords:** depression, antidepressant, prescribing, preferences, survey

## Introduction

Little is known with regards to which factors influence the antidepressant prescribing practices of clinicians when treating patients with major depressive disorder (MDD). Unfortunately, existing depression treatment guidelines such as those of the American Psychiatric Association (APA 2000) and of the Agency for Health Care Policy and Research (AHCPR- Mulrow et al 1999) do not offer an adequate framework for evaluating which treatment options are most efficacious. The APA's revised "Practice Guideline for the Treatment of Major Depressive Disorder" (APA 2000), for example, concludes that antidepressants appear to be equally effective for the treatment of MDD, and thereby suggest that the choice of antidepressants be based on considerations of their relative side-effect, safety, and tolerability profiles as well as their relative cost. Nevertheless, subsequent surveys indicate that a substantial proportion of practicing clinicians continue to believe that some antidepressants are more effective than others (Petersen et al 2002). In the absence of replicated clinical research guiding the choice of antidepressants, it is interesting to examine which factors clinicians take into account when selecting one agent over another. While a number of surveys have examined factors which influence clinician's selection of antidepressants (Olsson et al 1998; Hickie et al 1999; Garrison and Levin 2000; Petersen et al 2002), the majority of these reports focus on the presence of various illness characteristics (ie, depressive

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subtypes, neuro-vegetative symptom patterns), little is known regarding the role of drug characteristics (ie, efficacy, rapidity, safety, tolerability, and cost) as factors influencing clinicians when choosing among available antidepressants. The objective of this study is to gather data from a large group of clinicians on how their perceptions of the relative properties of antidepressants, including efficacy, rapidity of action, safety (ie, the likelihood of an antidepressant causing serious adverse events), tolerability (ie, the likelihood of treatment with an antidepressant being prematurely terminated due to uncomfortable side-effects) and cost, may influence their choice of antidepressants.

## Method

Clinicians attending the Massachusetts General Hospital annual psychopharmacology review course responded to a brief, anonymous questionnaire exploring how their perceptions of the relative properties of antidepressants influenced their choice of antidepressants. The administration of the questionnaire was approved by the Massachusetts General Hospital Institutional Review Board (IRB). A brief cover letter was attached to the questionnaire describing the voluntary research survey. No written consent was required. The questionnaire had two sections, and required approximately 5 minutes to complete. The first section elicited clinician responses with regards to their ranking of five antidepressant factors (efficacy, safety, tolerability, cost, and rapidity of action) influencing their choice of antidepressants. The second section contained hypothetical scenarios during which clinicians were asked to select the *minimal difference* in either response rates or the rapidity of response that they would require in order to choose one agent over another given differences in either their safety, tolerability, cost, or some combination of these factors. There were five possible responses to the questions regarding the *minimal difference* in response rates: a) 5%–10%, b) 10%–20%, c) 20%–30%, d) 30%–50%, and e) 50%+. There were four possible responses to the questions regarding the *minimal difference* in rapidity of response: a) 1–2 weeks, b) 2–3 weeks, c) 3–4 weeks, and d) 4+ weeks.

## Statistical tests

Clinician responses to those questions eliciting the minimal difference in response rates between two hypothetical antidepressants required in order to select one agent over another were ranked from 1 to 5 according to the magnitude of the difference in response rates from lowest (5–10%) to highest (50%+). Similarly, clinician responses to those

questions eliciting the minimal difference in rapidity of response between two hypothetical antidepressants required in order to select one agent over another were ranked from 1 to 4 according to the magnitude of the difference in rapidity of response from lowest (1–2 weeks) to highest (4+ weeks). Six (6) Wilcoxon signed rank tests were used to compare differences in response rank for each clinician between the four scenarios (1: comparable safety and tolerability and cost; 2: comparable safety and tolerability only; 3: comparable safety and cost only; 4: comparable tolerability and cost only). This was then repeated for those questions that substituted response rates for the rapidity of response as their outcome. We corrected for multiple analyses using the Bonferroni method (given a total of 12 analyses, statistical significance was set at  $p = 0.05/12 = 0.0042$  (two tailed) for each test).

## Results

### Sample characteristics

Two hundred seventy-three (273) of 682 (40.0%) of clinicians attending the course responded to the survey (57.1% women, mean age  $50.5 \pm 9.6$  years, completed training  $17.3 \pm 10.6$  years ago, average  $362.1 \pm 705.1$  patients treated per year). The respondent sample was composed largely of practicing clinicians, including 72.2% psychiatrists, 7.3% non-psychiatrist physicians, and 8.8% registered nurses. A little over 60% came from the Northeast and Mid-Atlantic states with the others representing a national and international (8.8%) distribution. 33.0% identified themselves as having special expertise in psychopharmacology, while 52.7% identified themselves as having expertise in both psychopharmacology and psychotherapy.

### Ranking of 5 antidepressant properties influencing antidepressant selection

When asked to rank 5 factors (efficacy, safety, tolerability, rapidity, and cost) for their relevance in influencing their decision-making when selecting an antidepressant, most clinicians chose efficacy as most relevant (57.3% or 152/265), followed by safety (23.0% or 61/265) tolerability (9.4% or 25/265), cost (5.2% or 14/265), and rapidity of action (4.9% or 13/265).

### Selecting minimal differences in efficacy as a function of safety, tolerability, and cost

Significant differences were found when we compared clinician responses when choosing the minimal difference in response rates required in order to select one hypothetical

antidepressant agent over another. Specifically, clinicians required smaller differences in response rates between two hypothetical agents with comparable safety, tolerability, and cost than two agents that differed in cost, tolerability, or safety. These results suggest that all three factors influence clinician treatment decisions. Similarly, clinicians required smaller differences in response rates between two hypothetical agents that differed in terms of cost than tolerability, or cost than safety. These results suggest that cost was less a consideration than either tolerability or safety. Finally, clinicians required smaller differences in response rates between two hypothetical agents that differed in terms of tolerability than safety, suggesting that tolerability was less of a consideration than safety. These results were replicated when the outcome was changed to the rapidity of response (see Tables 1 and 2).

## Discussion

The results of our survey reveal interesting findings on the relative role of the five antidepressant properties examined, namely efficacy, rapidity of action, safety, tolerability and cost, in influencing clinicians' decision-making when choosing antidepressants. Specifically, when asked to rank which of the five factors they are most likely to take into account when selecting one antidepressant over another, most ranked efficacy as most important followed by safety. Relatively few clinicians chose tolerability, rapidity of action, or cost as most important. This is of interest, given the fact that, as pointed out in recent reviews, several meta-analyses have called into question the magnitude of benefits derived from antidepressant treatment beyond placebo effects (Walsh et al 2002; Papakostas and Fava 2006). The emphasis on efficacy is also interesting given that true differences in efficacy across classes of antidepressants, although claimed, have been difficult to establish and there currently exist no reliable estimates for the magnitude of these potential inter-class differences

in clinical settings. In contrast, cost differences, which are readily quantifiable, do not appear to have a similar influence over antidepressant prescribing.

Despite this emphasis on efficacy, when presented with hypothetical scenarios in which there was a difference in efficacy between two antidepressant agents, clinicians reported that their relative safety and tolerability profiles as well as their cost were found to significantly influence their choices of one antidepressant over another. In fact, clinicians are more strongly influenced in their choice of antidepressants based on perceived differences in the safety profile of two agents than tolerability, and in perceived differences in tolerability than cost. For example, nearly two thirds of clinicians would choose an antidepressant with a 5%–20% greater response rate over another provided that these agents were comparable with respect to their safety, tolerability and cost. Similarly, if these agents were to differ in terms of their cost alone, approximately one in five clinicians would choose an agent with a 5%–20% greater response rate over another. Given a difference in tolerability profile alone, however, a little more than one-third of clinicians would choose an agent with a 5%–20% greater response rate over another agent over another, while approximately only one in six clinicians would make the same choice given a difference in safety profile alone.

In light of the lack of robust and replicated differences in efficacy between antidepressants or antidepressant classes, it is to be expected that cost, tolerability and, of course, safety have a strong influence on clinicians' decision-making. However, clinicians' perceptions regarding efficacy do not closely reflect the literature. For example, nearly 40% of clinicians require at least a 50% difference in response rates between two antidepressants in order to select the agent with the inferior safety profile (ie, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors), a staggering number given that the mean drug-placebo difference in antidepress-

**Table 1** Distribution of clinician responses: "What would be the minimal difference in response rates between two agents required in order for you to select one agent over another if those two agents possessed comparable...?"

	5%–10%	10%–20%	20%–30%	30%–50%	50%+
Safety, tolerability, cost*	27.8%	37.2%	23.6%	6.0%	5.2%
Safety, tolerability**	17.2%	35.7%	24.0%	17.2%	5.6%
Safety, cost†	12.7%	21.4%	27.0%	18.7%	19.9%
Tolerability, cost	9.0%	7.1%	21.8%	22.1%	39.4%

**Note:** \* $p < 0.0001$  when comparing the distribution in response rates between the top (equivalent safety, tolerability, and cost) and bottom three hypothetical scenarios.

\*\* $p < 0.0001$  when comparing the distribution in response rates between comparable safety/tolerability and comparable safety/cost.

\*\*\* $p < 0.0001$  when comparing the distribution in response rates between comparable safety/tolerability and comparable tolerability/cost.

† $p < 0.0001$  when comparing the distribution in response rates between comparable safety/cost and tolerability/ cost.

**Table 2** Distribution of clinician responses: "What would be the minimal difference in rapidity of response (in weeks) between two agents required in order for you to select one agent over another if these two agents possessed comparable...?"

	1–2 weeks	2–3 weeks	3–4 weeks	4+ weeks
Safety, tolerability, cost*	53.0%	36.4%	6.3%	4.1%
Safety, tolerability **	33.0%	39.4%	20.3%	7.1%
Safety, cost†	22.5%	25.9%	26.6%	24.8%
Tolerability, cost	18.4%	13.5%	23.6%	44.3%

**Note:** \* $p < 0.0001$  when comparing the distribution in response rates between the top (equivalent safety, tolerability, and cost) and bottom three hypothetical scenarios.

\*\* $p < 0.0001$  when comparing the distribution in response rates between comparable safety/tolerability and comparable safety/cost.

† $p < 0.0001$  when comparing the distribution in response rates between comparable safety/tolerability and comparable tolerability/cost.

‡ $p < 0.0001$  when comparing the distribution in response rates between comparable safety/cost and tolerability/ cost.

sant response rates was recently estimated as approximately 16.8% (Papakostas and Fava 2006). Similar findings were observed when we substituted clinical response with the rapidity of response as the main outcome. Almost 50% of clinicians responded that they would require a minimum of approximately 4 weeks difference in the rapidity of response between two antidepressants in order to choose an agent with an inferior safety profile. However, the development, in the near future, of antidepressants that are more effective than those currently available by 30%–50% is very unlikely. Nevertheless, smaller advantages in efficacy, some argue as small as a 10% difference in response rates (Cipriani et al 2006), may yield meaningful results in clinical practice. Therefore, better educating clinicians about the magnitude and relevance of any differences in efficacy between antidepressants would be necessary in order to ensure that depressed patients fully benefit from treatment.

One limitation of the present work is in the number of clinicians that responded to our questionnaire. Specifically, although there were 682 clinicians present at the time the questionnaire was administered, only 273 (40.0%) replied. Another limitation is the absence of questions that would reflect various gradients of difference in cost, tolerability and safety between two agents. In addition, no clarification was made if the agents were to be used as monotherapy or adjunctive therapy for depression, as first-line treatment or for treatment-resistant depression, or as an as an alternative treatment (switch) following intolerance to a given agent. In addition, the present questionnaire was not designed to take into account other factors influencing antidepressant prescription including patient preference, insurance coverage, personal history of response, family history of response, neuro-vegetative symptom pattern, psychiatric co-morbidity, or medical co-morbidity.

## Acknowledgments

Supported by NIMH Grant K23 MH069629 (GIP).

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