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Psychiatrists' Attitudes Towards Non-pharmacologic Factors within Context of Antidepressant Pharmacotherapy

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Abstract

Objective—Major depression is identified as prevalent, disabling, and a major determinant in the burden of disease. Recent meta-analyses of antidepressant clinical trials have suggested that up to 81% of response can be attributed to non-medication related factors. This study examined psychiatrist's attitudes and beliefs towards non-pharmacologic factors within the context of antidepressant pharmacotherapy.

Methods—Using a web-based tool, an anonymous 5-minute, 20-question cross-sectional survey was distributed to 100 staff psychiatrists and 60 psychiatry residents at an academic hospital in Boston, Massachusetts. Participant demographics, practice characteristics, beliefs about non-pharmacologic factors affecting prescribing practices, and opinions about the need for further investigations in the psychopharmacology process were assessed.

Results—There was an overall response rate of 58%; the final sample included 79 responses and consisted of an even distribution for gender and years of clinical experience compared to non-responders. While the medians for patients response and remission rates (54% and 33%, respectively) were in agreement with published rates, median of the portion of clinical outcomes due to placebo effects was only 26%, numerically less than suggested by literature. The contribution of the active ingredients of medications was perceived to be significantly higher than the contribution of patient characteristics ($t = 3.73$; $df = 75$, $p = .000$) and clinician characteristics ($t = 8.70$; $df = 75$, $p < .001$). A longer time since graduation from medical school was significantly associated with higher belief in the effect of the active ingredients of anti-depressant medications ($r = .380$, $p < 0.01$).

Conclusion—These findings highlight the discrepancy between empirical evidence and psychiatrists beliefs on the impact of non-specific effects on clinical outcomes. Educating antidepressant prescribers about the evidence base on psychosocial mediators of placebo effects

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contribution to outcome may represent an economically favorable strategy for improving clinical outcomes.

Keywords

depressive disorder; physician's practice patterns; antidepressants; contextual factors

Introduction

Affecting 298 million worldwide, major depression is identified as prevalent, disabling, and a major determinant in the burden of disease (1). Mono-aminergic antidepressant medications are widely prescribed but only moderately effective for the majority of patients (2). The limitations of current antidepressant pharmacotherapies highlight the urgent public health need for alternative outcome-enhancing and cost-effective interventions. Several independent-sample meta-analyses of antidepressant clinical trials have suggested that up to 81% of response can be attributed to non-pharmacological factors, many of which remain unknown (3–6). Researchers have demonstrated that these nonspecific factors such as degree of involvement of patient in decision-making (7–10), physician communication (11–15), therapeutic alliance (16–18), patient expectations (19–28), patient preferences (29–33), and contact frequency (34) may affect clinical outcomes, especially in milder forms of depression. Furthermore, a re-analysis of a naturalistic study comparing imipramine to placebo demonstrated that psychiatrists were responsible for more variance in outcomes than treatment suggesting that effective psychiatrists can augment the effects of the active ingredients of antidepressant medications (35).

There has been a recent revived interest in placebo response within the scientific community, especially within psychiatry (36). However, much of the published work has focused on neurobiological mechanisms with less attention given to psychological mechanisms. While we now understand that placebo responses produce measurable changes in brain activity that overlap with medication-induced improvement (37), it remains unclear how these elucidated neurobiological mechanisms can be used to develop accessible tools for practitioners looking to activate placebo responses in their patients.

A series of cross-sectional surveys have demonstrated that a large portion of physicians including psychiatrists prescribe impure placebos, defined as substances with pharmacological effect but not on condition being treated (38–44). Psychiatrists were more likely to believe that placebos had clinical effects compared to non-psychiatrists (45). However, deceptively prescribing placebos remains controversial and ethically problematic. As such, utilizing the underlying factors of placebo effects when actively prescribing evidenced-based antidepressants may represent a viable alternative. No previous studies have explored psychiatrists' attitudes toward these non-specific factors. For these reasons, we aimed to assess the beliefs and attitudes of psychiatry trainees and staff psychiatrists toward the above-noted contextual factors. We hypothesized that a large portion of antidepressant prescribers are unaware of this data as it is primarily studied in the psychology literature. Accordingly, we suspect a notable under-appreciation of placebo

effects in antidepressant pharmacotherapy. We also hypothesize that more experienced clinicians would indicate a greater importance of non-pharmacological factors.

Methods

Study Participants and Setting

Using departmental email distribution lists, we distributed a cross-sectional, web-based survey (Qualtrics©) among 100 staff psychiatrists and 60 psychiatry post-graduate trainees affiliated with the psychiatry department of Harvard Medical School in Boston, Massachusetts. Eligible participants were post-graduate trainees (PGY-1 through PGY-6) in an ACGME-accredited psychiatry program. Subjects were ineligible, if they were not prescribing standard antidepressants (SSRIs, TCAs, MAOIs). This study was approved by the institutional review board at Brigham and Women's Hospital. Informed consent was received from all respondents. Original data was collected between July and August 2014.

Measures

The 20-item survey was completed anonymously and took approximately 5 minutes to complete. It included participant demographics, practice characteristics, beliefs about factors affecting prescribing practices, and opinions about the need for further investigations in the psychopharmacology process. To assess prescribers' perceptions about response and remission rates for their own patient panels, we asked two separate questions with responses in ten percent increments (0–10%, 11–20%...91–100%). Definitions for response and remission were provided within the prompts. In a separate question, respondents were asked to quantify their perception of what percent of antidepressant response is due to placebo effects versus active ingredients of antidepressants; possible responses also ranged from 0–10% to 91–100% in ten percent increments. Prescribers were further asked about how much time they spent discussing risks and benefits prior to recommending initiation of treatment with an antidepressant. Answer choices were in five minute increments ranging from 0–5 minutes to greater than 31 minutes. A similar question was asked inquiring the length of routine prescribers' routine psychopharmacology follow-up visits for patients with depression. Respondents were asked if their prescribing practices had changed based on the recent meta-analyses questioning the clinically relevant efficacy of antidepressants. Of those who responded yes, a follow-up question asked whether they increased or decreased their likelihood to prescribe antidepressants.

In the second part of our survey, we asked providers to quantify their beliefs about relative contributions of the following factors on treatment outcomes: therapeutic alliance, active ingredients of antidepressants, patient characteristics, and clinician characteristics (36, 46). Total contributions were required to equal 100%. To gain perceptions about individual patient factors (expectations of treatment, treatment preferences, ambivalence about medications, readiness to change) and clinician factors (attitude of prescriber, prescriber communication style, involvement of patient in decision-making, instillation of hope, and contact frequency), two subsequent questions were asked in the same format. The final 3 questions of the survey asked prescribers their opinions on the clinical relevance of placebo effects on a 5-point likert scale (strongly agree, agree, neutral, disagree, strongly disagree).

Statistical Analyses

Because overall percentage of missing values was < 10%, we did not impute missing values. Absolute and relative frequencies were used to display the distribution of categorical data and the median was used to describe ordinal variables. Mean and standard deviation were used to describe parametric variables. Correlations between variables were tested using spearman's correlation coefficient, since the majority of the variables were ordinal data. Differences in perceptions among the relative contributions of general factors, clinician factors and patient factors were tested using within-subjects ANOVA. Significant main effects were followed-up with post-hoc *t*-tests between the individual factors of each category applying bonferroni correction for multiple testing. All analysis were carried out using SPSS 22.

Results

Ninety-three surveys were returned for an overall response rate of 58% (62% for trainees and 56% for staff psychiatrists). A total of 13 subjects were removed from the analyses because they only submitted responses for demographical data and 1 subject was removed because his responses indicated an invalid response pattern (the most extreme answer on every question). The final sample contained $n=79$ subjects. Demographic and work related characteristics of participating psychiatrists can be found in Table 1. Notably, the sample consists of an even distribution of male and female psychiatrists, Further, there is a broad distribution along different career stages (Years since med school, % trainees, PGY). Only a few participants were not primarily working at an academic medical center. Median length of routine psychopharmacological visits was 26–30 minutes, median time spent discussing risks and benefits was 6–10 minutes, and median visit frequency for acutely depressed patients was every 2 weeks.

Beliefs about personal response and remission rates as well as psychiatrists' beliefs about what portion of treatment outcome can attributed to placebo effects can be found in Table 2. The median for perceived response rates and remission rates were 54% and 33% respectively. However, median of the portion of clinical outcomes attributed to placebo effects was 26%. While, 96.2% of respondents reported familiarity with the recent literature questioning the efficacy of anti-depressant medication, only 23.1% stated that these writings have influenced their prescribing practices. Among those reported changing their prescribing practice, 80.0% decreased their anti-depressant prescriptions. Psychiatrists who reported increasing their tendency to prescribe antidepressants ($n=3$) rated more favorably the importance of medication effects ($M=46.67$; $SD=25.17$) than those who reported decreasing their prescribing practices ($M=26.67$; $SD=10.52$). Further, 96% of the sample agreed or strongly agreed that enhancing therapeutic components that contribute to placebo responsivity may be a clinically appropriate way of improving clinical outcomes and 93% agree or strongly agree that placebo response in antidepressant treatment is worthy of scientific investigation as it has the potential to illuminate the pathophysiology of depression. Psychiatrists' beliefs of the relative contributions of general factors affecting pharmacotherapy outcomes and perceptions of patient-related and clinician-related factors can be seen in Table 3. There was a significant difference among the perceived contribution

of general treatment factors ($F_{3, 73} = 29.69, p = .000$). The contribution of the active ingredients of medications was perceived to be significantly higher than the contribution of patient characteristics ($t = 3.73; df = 75, p = .000$) and clinician characteristics ($t = 8.70; df = 75, p < .001$). Further, the contribution of therapeutic alliance was perceived to be significantly higher than the contribution of patient characteristics ($t = 2.91; df = 75, p = .030$) and clinician characteristics ($t = 8.99; df = 75, p = .000$). Last, patient characteristics' contribution was perceived significantly higher than clinician characteristics ($t = 7.02; df = 75, p = .000$). There was no significant difference among the other possible combinations.

Among patient-related contextual factors, there was a significant difference in the perceived relative contribution to treatment outcome ($F_{3, 71} = 29.69, p = .000$). The relative importance of patients' expectations was perceived as significantly more important than inquiry of patient's treatment preferences ($t = 4.43; df = 73, p = .000$), and significantly more important than the assessment of patients' ambivalence towards medication ($t = 3.71; df = 73, p = .002$). Further, readiness to change was felt to be significantly less relevant to outcomes than patients' treatment preferences ($t = 2.71; df = 73, p = .048$) and ambivalence towards medication ($t = 2.73; df = 73, p = .048$). There was no significant difference among the other possible combinations. Additionally, there was no significant difference among the relative contributions of the clinician-related factors ($F_{4, 71} = 2.35, p = .068$).

Associations between practice characteristics and psychiatrists' perceptions can be seen in Table 4. A longer time since graduation from medical school was significantly associated with higher perceived response and remission rates and a higher belief in the effect of the active ingredients of anti-depressant medications. It was further inversely related to the perceived importance of placebo effects and patient characteristics in anti-depressant treatment. Among the level of trainees, a similar pattern was observed. Higher trainee-level (PGY) was significantly associated with higher perceived response rate ($r = .431, p = .040$) and higher perceived importance of active pharmacological ingredients ($r = .498, p = .018$). Higher PGY was related to less perceived importance in the instillation of hope ($r = .469, p = .028$). Further, length of routine visits is significantly associated with lower perceived importance of patient and clinician characteristics. Longer time discussing risks and benefits of anti-depressants is associated with lower perceived importance of patient characteristics. Finally, higher reported response and remission rates are significantly associated with less frequent follow up visits.

Discussion

Our findings demonstrate that post-graduate trainees in psychiatry and staff psychiatrists at a Harvard-affiliated program under-appreciate the impact of placebo effects on clinical outcomes for patients receiving antidepressants for major depression. Respondents reported their belief that 26% percent of clinical antidepressant response is due to non-pharmacologic or placebo effects. Notably, various meta-analyses have suggested that up to 67–81% of clinical response in antidepressant trials may be attributable to non-medication related effects (3–6). This discrepancy may be due to prescribers' lack of familiarity with these data even though 96.2% of respondents reported that they had read these studies. Alternatively, differences in operational definitions of 'placebo effects' may account for some of the

variance. Respondents may have considered data from naturalistic, wait-list control studies suggesting that approximately 25% to 33% of improvement occurring with medication treatment in clinical trials can also be seen in wait-list control conditions due to spontaneous remission, natural waxing and waning of symptoms and regression-to-the mean. (47). Further, measurement factors as well as natural history factors are known to contribute to observed placebo response (36). Among general factors affecting pharmacotherapy outcomes, subjects placed statistically significant importance on the relative contribution of the active ingredients of medications in comparison to patient characteristics and clinician characteristics. This finding further highlights the weight that clinicians place on antidepressant sometimes at the expense of other interactional and expectancy-based factors.

Clinical experience, measured by years since medical school graduation, was interestingly associated with higher belief in the relative contribution of medication effects. A similar pattern was seen among trainee level. If corroborated in future studies with larger, more representative sample, this may present an opportunity for continuing medical education programs. Evidenced-based treatments hold promise only if clinicians implement them. While passive approaches to training physicians (e.g. workshops, manuals), may increase provider knowledge, literature shows that they do not consistently lead to provider behavior change (48). Research in innovative teaching methods will be needed to promote the implementation of empirically supported treatment strategies. Enhancing awareness of these contextual factors among antidepressant prescribers may represent a strategy for improving outcomes for available treatments for Major Depressive Disorder at a time when the pipeline for novel non-mono-aminergic antidepressants is underwhelming. Systematic psychopharmacology process investigations may impart opportunities to translate the psychological components of placebo response into concrete clinical interventions (e.g., how best to communicate expectations to patients in ways that have therapeutic efficacy without deception).

Our findings must be interpreted in the context of the limitations of our study. Our survey was conducted with a relatively small sample size of psychiatrists at an academic medical center and may not be representative of the general population of antidepressant prescribers, of which the majority comprises of primary care physicians. Our sample, however, did include an even distribution of men and women at a broad distribution of stages in their careers and perceived response and remission rates matched that of extant literature (36, 49). Prior studies have demonstrated that psychiatrists seem to better value the influence of placebo effects in comparison to other physicians (45). Our sample was from a single academic center in a region within the United States that may be more likely to consider placebo effects in their prescribing practices compared to academic psychiatrist from more biologically-driven departments in other geographically regions (50). In addition, while the majority of psychiatrists practice within the community, our sample consisted of academic physicians. We were unable to find previous studies reporting the variation in prescribing patterns between academic and community psychiatrists. Future questionnaire studies should include primary care providers, community psychiatrists, and an academic comparator group from a different geographical region. Because of our small sample size, we recognize that we may have not had power to detect other factors influencing beliefs about treatment effects. We cannot be certain of how survey respondents differed from non-

respondents or the degree to which response bias may have influenced our reported findings. Finally, we do not know the degree to which respondents responses on the relative importance of contextual factors reflects their actual decision-making and behaviors in the clinical setting.

Conclusion

The under-appreciation of the importance of placebo effects represents a significant gap in knowledge among antidepressant prescribers. Educating prescribers about the evidence base on psychosocial mediators of placebo effects may represent an economically favorable strategy for improving clinical outcomes. Further investigations in psychopharmacology research exploring psychological processes associated with clinical improvement are warranted.

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Table 1
Demographic and work related characteristics of participating physicians N=79.

Age M (SD) (MD=18)	43.88 (14.66)
Sex f (%) female	41 (51.9)
Years since graduation M (SD) (MD=1)	16.68 (13.85)
Trainee f (%)	33 (41.8)
PGY f (% of trainees) (MD=17)	
PGY-1	0 (0.0)
PGY-2	3 (18.8)
PGY-3	9 (56.3)
PGY-4	3 (18.8)
PGY-5	0 (0.0)
PGY-6	1 (6.3)
Employment setting f (%)	
Academic medical center	69 (87.3)
Other	10 (12.7)
Time discussing risks and benefits of antidepressants f (%) (MD=3)	
0-5 min	17 (22.4)
6-10 min	35 (46.1)
11-15 min	12 (15.6)
16-20 min	8 (10.5)
21-25 min	2 (2.6)
26-30 min	1 (1.3)
>31 min	1 (1.3)
Length of routine visits f (%) (MD=4)	
0-5 min	0 (0.0)
6-10 min	3 (4.0)
11-15 min	2 (2.7)
16-20 min	14 (18.7)
21-25 min	16 (21.3)

26–30 min	30 (41.3)
>31 min	9 (12.0)
Frequency of follow-ups for acutely depressed (mild to mod) patients f (%) (MD=4)	
every week	23 (23.7)
every 2 weeks	26 (34.7)
every 2–4 weeks	24 (32.0)
> every 4 weeks	2 (2.7)

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Table 2

Perceptions about psychopharmacological treatments (N=79)

	Response rate f (%) (MD=4)	Remission rate f (%) (MD=4)	Outcome due to placebo effects f (%) (MD=3)
<i>Mdn</i>	54%	33%	26%
0–10%	0 (0.0)	0 (0.0)	6 (7.9)
11–20%	0 (0.0)	11 (13.9)	9 (11.8)
21–30%	5 (6.7)	13 (16.5)	23 (30.3)
31–40%	5 (6.7)	19 (25.3)	19 (25.0)
41–50%	10 (13.3)	8 (10.7)	11 (14.5)
51–60%	21 (28.0)	9 (12.0)	5 (6.6)
61–70%	18 (22.8)	9 (12.0)	3 (3.9)
71–80%	13 (16.5)	4 (5.3)	0 (0.0)
81–90%	2 (2.5)	2 (2.7)	0 (0.0)
91–100%	1 (1.3)	0 (0.0)	0 (0.0)

Perceptions about the relative contributions of treatment related factors to treatment outcome.

Table 3

General factors (MD=3)	M (SD)
Therapeutic alliance	30.37 (13.03)
Active pharmacological ingredient	32.71 (14.63)
Patient characteristics	23.55 (10.83)
Clinician characteristics	13.63 (7.42)
Clinician Factors (MD=4)	
Attitude	20.40 (11.53)
Communication style	20.73 (9.85)
Involvement of Patient in decision-making	21.73 (12.37)
Instillation of hope	20.33 (8.03)
Contact frequency	16.47 (8.62)
Patient factors (MD=5)	
Expectations of treatment	30.38 (13.96)
Treatment preferences	21.01 (8.99)
Ambivalence about medications	21.62 (9.15)
Readiness to change	26.86 (12.81)

Table 4
Associations between professional characteristics and perceptions about anti-depressant treatment.

	Years since graduation	Sex	Time discussing risk and benefits	Length of routine visits	Frequency of follow ups
Response rate	.406**	-.217	.060	.171	-.230*
Remission rate	.469**	-.241*	.148	.143	-.242*
% outcome due to placebo effects	-.274*	-.042	-.165	-.079	.068
Therapeutic Alliance	-.214	.241*	-.043	.072	.103
Active medications	.380**	-.205	.177	.176	-.177
Patient Characteristics	-.274*	.001	-.167	-.316**	.019
Clinician Characteristics	-.192	-.107	-.234*	-.250*	.140
Attitude	.110	-.124	-.110	.012	.068
Communication style	.010	-.083	.231	.096	-.148
Involvement of Patient in decision-making	-.050	.027	-.085	-.180	-.015
Instillation of hope	-.118	-.156	-.106	-.175	.095
Contact frequency	-.045	-.035	-.143	-.114	.188
Expectations of treatment	.088	-.033	.093	.138	-.166
Treatment preferences	.014	-.321**	-.222	-.004	.123
Ambivalence about medications	-.050	.077	-.066	-.145	-.105
Readiness to change	-.123	.115	.067	-.160	.108

Notes.

* $p < .05$.

** $p < .01$.