Psychiatr. Pol. 2018; 52(6): 957–969
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/98961

Increase in pharmacodynamic tolerance after repeated antidepressant trials in treatment-responsive bipolar II depressed subjects: An exploratory study

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Summary

Objective. This study examined the presence of increased pharmacodynamic tolerance with reduced effectiveness following repeated antidepressant trials over the course of the affective illness in subjects with treatment-responsive bipolar II depression.

Methods. Data were derived from the open-label phase of a prospective, randomized, placebo-controlled trial of long-term fluoxetine versus lithium monotherapy in 148 subjects ≥18 years old with treatment-responsive bipolar II depression, who were initially administered open-label fluoxetine monotherapy for 12 weeks. Response was defined as ≥50% reduction in baseline Hamilton Rating Scale for Depression (HRSD) score, and remission was defined as a final HRSD score ≤8.

Results. Subjects reported a mean (SD) total of 1.61 (1.85) (range: 0–9) prior adequate, antidepressant trials over the course of their affective illness, before study enrollment. There was a 25% reduction in the likelihood of fluoxetine response ($p < 0.01$) and a 22% lower likelihood of remission ($p = 0.02$), respectively, with each increase in the number of prior antidepressant treatment trials over the illness course. There was no clinically meaningful correlation between fluoxetine response or remission and any other baseline clinical or demographic variable. Thus, only the number of prior antidepressant trials meaningfully impacted the likelihood of fluoxetine response or remission.

Limitations. This was an exploratory study of post hoc, analyses, and the trial was not specifically powered to test the development of increased pharmacodynamic tolerance. Disease heterogeneity or inter-individual differences in antidepressant responsiveness may have influenced fluoxetine effectiveness.

Conclusion. These results confirm prior observations of an increased pharmacodynamic tolerance after repeated antidepressant administration, resulting in a step-wise loss of antidepressant effectiveness over the course of the illness.

Key words: drug tolerance, tachyphylaxis, fluoxetine

Introduction

An increase in pharmacodynamic tolerance of antidepressant drugs with a loss of effectiveness was first suggested by Lieb and Balter [1] and subsequently demonstrated by Amsterdam et al. [2] in a prospective study of 149 fluoxetine-treated subjects with unipolar or bipolar II major depressive episode. Further studies appeared to confirm these initial findings and suggested the presence of a 20–50% step-wise loss of effectiveness with each increase in the number of prior antidepressant trials ([3–7]; see also [8–11]). The phenomenon has been reported in unipolar depression [2, 3, 5, 6] but may also occur in bipolar disorder [3, 4, 7], and may be more common with repeated administration of selective serotonin reuptake inhibitor (SSRI) antidepressants [12–14], although it may also occur with other pharmacologic classes of antidepressants [3, 4, 8–10]. One study reported that the loss of response may be specific to antidepressant drugs per se, with response to psychotherapy not affected by prior antidepressant exposure [6].

There is considerable debate as to whether step-wise loss of antidepressant effectiveness results from a genetic predisposition to non-response [13, 15, 16] or from oppositional tolerance with a persistant induction of monoamine receptor down-regulation by repeated antidepressant administration [17]. The latter possibility is particularly disturbing because it would suggest that some cases of resistant depression may be iatrogenic in nature and result from repeated antidepressant administration per se, but not from the application of psychotherapy [6].

While the multi-level Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [11] reported a cumulative remission rate of 67%, this figure obscured the presence of a step-wise reduction in antidepressant effectiveness with each increase in the number of prior antidepressant treatment trials [8–11]. Thus, while remission rates during the STAR*D study declined from 36.8% to 30.6% in subjects receiving 0 or 1 prior antidepressant trials, respectively; the remission rates fell to 13.7% and 13.0% in subjects who previously received 2 or more prior antidepressant trials, respectively [8–10]. Moreover, STAR*D subjects who required more antidepressant trials to achieve remission also demonstrated greater relapse rates during follow-up evaluation [11].

In the current exploratory analysis, we examined the phenomenon of increased pharmacologic tolerance after repeated exposure to antidepressant therapy administered at any time over the course of the affective illness, from data derived from a prospective randomized controlled trial of fluoxetine monotherapy of bipolar II major depressive episode. The primary aim of the current study was to examine whether or not an increase in the number of prior antidepressant trials was associated with a step-wise reduction in the likelihood of response and remission to acute fluoxetine monotherapy in bipolar II major depressive episode.

Material and methods

Subjects

Data for this exploratory analysis were derived from the open-label phase of a randomized placebo-controlled comparison of fluoxetine versus lithium monotherapy for bipolar II depression. The primary study outcomes and design features have been described elsewhere [18, 19]. Briefly, outpatient subjects ≥ 18 years old were included if they met DSM IV-TR criteria for bipolar II disorder and a current major depressive episode via the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) [20]. Subjects had a minimum 17-item Hamilton Rating Scale for Depression (HRSD) [21] score ≥ 16.

Exclusion criteria were: history of prior mania or psychosis, substance use disorder within the preceding 3 months, sensitivity or non-response to fluoxetine within the current episode, unstable medical condition, or concurrent use of antidepressant or mood stabilizer medication.

Procedures

Informed consent was obtained in accordance with the ethical standards of the Institutional Review Board, using Good Clinical Practice guidelines [22] with oversight by the local Office of Human Research and an independent Data and Safety Monitoring Board.

Best estimates of the number of prior DSM IV defined major depressive and hypomanic episodes since the onset of the disorder were obtained at baseline from subjects using SCID format. Best estimates of prior, adequate antidepressant, mood stabilizer, and other psychotropic drug therapy during the current and prior affective episodes was ascertained via the SCID format [20] and available medical and pharmacy records. Adequacy of prior dosage and treatment duration was ascertained using an adaptation of the Harvard Antidepressant Treatment History of the SCID [23, 24]. Trials of unverified adequacy were excluded; while trials of borderline adequacy were individually examined by the investigators for consensus determination.

Treatment procedures

Fluoxetine monotherapy was initiated at 20 mg daily and increased by 10–20 mg every other week to a maximum dose of 80 mg daily by week 6 of treatment. The dose could be reduced to a minimum of 10 mg daily depending upon response and tolerability. Subjects unable to tolerate 10 mg daily were discontinued from the trial. Response was defined as a ≥ 50% reduction in baseline HRSD score by treatment week 10 with a final HRSD score ≥ 9. Remission was defined as a ≥ 50% reduction in baseline HRSD score plus a final HRSD score ≤ 8 at treatment week 6, 8, or 10, which

was maintained for 2 additional weeks of consolidation therapy. Non-response was defined as < 50% reduction in baseline HRSD score by treatment week 10. Structured 17-item HRSD and Young Mania Rating Scale (YMRS) [25] measures were obtained by a study clinician at treatment weeks 1, 2, 4, 6, 8, 10, 11, and 12.

Statistical procedures

Analyses were conducted using the R programming language [26]. Missing data on outcomes were analyzed using the last observation carried forward principle. Initial analyses summarized baseline demographic and clinical variables. Outlier values ≥ 3 standard deviations (SD) above the mean were winsorized.

To assess the influence of demographic and clinical variables on the number of prior antidepressant trials ascertained at baseline, we examined product moment correlations between the number of prior antidepressant trials and that of the continuous variables; as well as the point-by-serial correlations between the number of prior antidepressant trials and binary variables.

The primary outcome variables were fluoxetine response versus non-response, and fluoxetine remission versus non-remission. We initially analyzed these values with logistic regression models, regressing response and remission on the number of prior antidepressant trials. Next, we repeated these analyses regressing response and remission on the number of prior antidepressant trials while controlling for the measured demographic and clinical variables: sex, race (White/non-White), rapid cycling status (yes/no), age, age of onset of first depression, age of onset of first hypomania, baseline HRSD, duration of current depressive episode, number of prior antidepressants, and number of prior hypomanic episodes. We repeated these analyses to explore the effect of specific medication classes.

Results

Baseline Clinical & Demographic Features

Initially, 167 subjects were enrolled. Nineteen subjects (11.4%) were screen failures; and 148 subjects received open-label fluoxetine for at least one post-baseline measurement.

54.1% of the participants were women with mean (SD) age 37.46 (13.41) years; and 46.7% were men with mean (SD) age 36.91 (12.73) years. Table 1 displays other demographic and clinical features of the sample. Table 2 displays the frequency of various pharmacologic antidepressant drug classes administered prior to study enrollment.

Table 1. **Baseline characteristics of bipolar II subjects who received fluoxetine therapy (n = 148)**

	%	n
Male	45.90%	68
White	76.40%	113
Rapid cycling	25.00%	37
	M	SD
Age	37.21	13.06
Onset depression	19.18	7.89
Onset hypomania	21.80	8.13
Baseline HRSD	22.03	3.61
Duration MDE (mo.)	12.58	15.43
# prior MDEs	8.76	19.46
# prior hypomania	15.14	29.21

HRSD – Hamilton Rating Scale for Depression; MDE – major depressive episode; Mo. – months

Table 2. **Number of prior antidepressant trials for bipolar II subjects treated with fluoxetine**

Specification		n	%
Any antidepressant	0	55	37.2
	1	32	21.6
	2	26	17.6
	3	9	6.1
	4	12	8.1
	5	6	4.1
	6+	8	5.4
SSRI	0	66	44.6
	1	39	26.4
	2	28	18.9
	3+	15	10.1
SNRI	0	118	78.7
	1+	30	21.3
TCA	0	136	91.5
	1+	12	8.4
Others	0	113	76.4
	1+	35	23.6

SSRI – selective serotonin reuptake inhibitor; SNRI – serotonin and norepinephrine reuptake inhibitors; TCA – tricyclic antidepressant; MAOI – monoamine oxidase inhibitor; Others – e.g., bupropion, mirtazapine, trazodone, etc.

Overall, subjects received a mean (SD) total of 1.61 (1.85) (range: 0–9) prior adequate antidepressant trials, which we coded as 0, 1, 2, 3, 4, 5, 6+. Table 3 displays the correlations between the number of prior antidepressant trials and baseline demographic and clinical variables.

Table 3. **Clinical and demographic correlates of number of prior antidepressant trials**

Specification	Total	SSRIs	SNRIs	TCAs	Others
Male	-0.09	-0.07	-0.01	-0.09	-0.05
White	0.12	0.01	0.20	0.06	0.16
Rapid cycling	-0.09	0.02	-0.14	-0.16	-0.13
Age	0.19*	0.05	0.20*	0.22**	0.18*
Onset depression	0.08	-0.07	0.09	0.11	0.19*
Onset hypomania	0.15	-0.02	0.15	0.25**	0.18*
Baseline HRSD	0.10	0.16	-0.04	-0.08	0.05
Duration MDE	0.04	-0.04	0.01	0.14	0.07
# prior MDEs	-0.08	-0.04	-0.06	-0.05	-0.07
# prior hypomania	-0.04	0.00	-0.06	-0.05	-0.07

*p < 0.05; ** p < 0.01; HRSD – Hamilton Rating Scale for Depression; MDEs – major depressive episodes

Correlations between the number of prior antidepressant trials and baseline demographic and clinical variables were generally insignificant. However, there was a statistically significant positive correlation between the number of prior antidepressant trials and subject age ($r_{148} = 0.19$; $p = 0.02$). There was also a statistically significant correlation between the age of onset of the first hypomanic episode and whether they had ever been treated with a tricyclic antidepressant (TCA) ($r_{148} = 0.22$; $p = 0.008$), or whether they had ever been treated with an antidepressant classified as "other" (such as bupropion or mirtazapine ($r_{148} = 0.18$; $p = 0.03$).

Effect of prior antidepressant trials on fluoxetine response

The number of prior antidepressant trials was negatively associated with the odds of current fluoxetine response (OR = 0.77; 95% CI = 0.55–0.94; B = – 0.25; SE = 0.10; $z = -2.64$; $p < 0.01$) and remission (OR = 0.81; 95% CI = 0.60–0.97; B = – 0.22; SE = 0.10; $z = -2.25$, $p = 0.02$). A similar pattern was obtained when we controlled for sex, race, rapid cycling status, age, age of onset of first depression, age of onset of first hypomania, baseline HRSD, duration of current depressive episode, number of prior antidepressants, and number of prior hypomanic episodes.

The number of prior antidepressant trials was associated with a 25% reduction in the odds of fluoxetine response (OR = 0.77; 95% CI = 0.51–0.92; B = – 0.29;

SE = 0.11; $z = -2.72$; $p < 0.01$) and a 22% reduction in the odds of fluoxetine remission (OR = 0.78; 95% CI = 0.55–0.96; B = – 0.25; SE = 0.10; $z = -2.38$; $p = 0.02$). No other variable predicted response or remission at $p < 0.05$; although trends in the data suggested higher rates of response and remission among Caucasian subjects and those with more recurrent histories of depression ($p > 0.07$).

Effect of prior pharmacologic class on fluoxetine response

After controlling for sex, race, rapid cycling status, age, age of onset of first depression, age of onset of first hypomania, baseline HRSD, duration of current depressive episode, number of prior antidepressants, and number of prior hypomanic episodes,the number of prior SSRI trials per se were not significantly associated with current fluoxetine response (OR = 0.73; 95% CI = 0.43–1.11; B = – 0.32; SE = 0.31; $z = -1.48$; $p = 0.48$) or remission (OR = 0.78; 95% CI = 0.50–1.18; B = – 0.24; SE = 0.21; $z = -1.18$; $p = 0.24$).

Prior treatment with TCAs or other antidepressants was not associated with current fluoxetine response or remission ($p > 0.87$); In contrast, the number of prior serotonin/noradrenalin reuptake inhibitor (SNRI) trials was associated with a significantly reduced odds of fluoxetine response (OR = 0.33; 95% CI = 0.07–0.88; B = – 1.12; SE = 0.51; $z = -2.21$; $p = 0.03$) and remission (OR = 0.35; 95% CI = 0.08–0.94; B = – 1.06; SE = 0.51; $z = -2.09$; $p = 0.04$). Most subjects without a prior history of SNRI exposure experienced response (70%) or remission (64%). However, subjects who had prior exposure to a SNRI were less likely to respond to fluoxetine (40%, $x^2(1) = 8.98$; $p = 0.003$) or remit (40%, $x^2(1) = 7.11$; $p = 0.008$).

Discussion

Results from this study support growing evidence that an increased pharmacodynamic tolerance, with a step-wise loss of antidepressant effectiveness, may occur with each increase in the number of prior antidepressant treatment exposures administered over the course of the affective illness, in patients with previously treatment-responsive unipolar and bipolar II depression [2–10]. This phenomenon, albeit controversial, may be substantially responsible for the low rate of antidepressant effectiveness after repeated trials of antidepressant therapy during recurrent depressive episodes, and may also contribute to the increased prevalence of treatment-resistant depression [27, p. 170]. Although concerted efforts have been made to develop new antidepressants with novel mechanisms of action that may be more effective than currently available drugs, the promise of achieving greater effectiveness with these agents has not been realized, and the prevalence of persistent depression appears to be increasing [27, pp. 148–171].

Our current observation of reduced response and remission rates associated with repeated antidepressant administration comports with prior findings by our group of

step-wise loss of antidepressant effectiveness after repeated antidepressant treatment trials [2–7]. Although some investigators have suggested that this phenomenon may result from a higher frequency of prior depressive episodes, greater symptom severity, longer illness length or episode duration (among other factors), current and previous analyses by our group have not demonstrated a statistically significant or clinically meaningful association between any baseline clinical or demographic variable and treatment response, save that of the number of prior antidepressant treatment trials [2–7]. Thus, the phenomenon of increased pharmacodynamic tolerance after repeated antidepressant administration appears to be statistically associated with only the number of prior antidepressant trials [2–7].

For example, one study [5] examined 276 treatment responsive subjects with unipolar major depression who received sertraline 150–200 mg daily for 8 weeks, and those with inadequate response were randomized to continuation therapy with either sertraline plus atomoxetine ($n = 72$) or sertraline plus placebo ($n = 74$) for 8 additional weeks. Logistic regression found a negative association between the number of prior antidepressant treatment trials and the odds of response to initial sertraline treatment ($p = 0.0035$), indicating a 19.9% reduction in the odds of response to sertraline with each increase in the number of prior antidepressant trials. In contrast, there was no relationship between the number of prior antidepressant trials and response to sertraline plus placebo or sertraline plus atomoxetine.

Another study of patients with treatment-resistant unipolar or bipolar depression, showed an even greater magnitude of tolerance (with loss of antidepressant effectiveness) [3]. In this study, we examined the odds of response and remission to monoamine oxidase inhibitor (MAOI) therapy in 59 subjects who were unresponsive to as many as 15 prior antidepressant trials in the current depressive episode. We found a significant negative correlation between the number of prior antidepressant trials and the odds of MAOI response, which decreased by a factor of 32% with each increase in the number of prior antidepressant exposures. In contrast, there was no significant association between age, gender, illness duration, episode length, or MAOI dose and the odds of MAOI response [3]. These results comport with observations from the latter treatment levels of the STAR*D study showing a dramatic reduction in the odds of response and remission to increasingly aggressive antidepressant treatment trials (including that of MAOI therapy) [9, 11].

Finally, a study by Leykin et al. [6] comparing cognitive therapy to paroxetine therapy or pill placebo showed that increased tolerance after repeated antidepressant administration was limited to paroxetine per se, and did not affect response to cognitive therapy. This finding suggests that psychotherapy may exert its therapeutic action via a mechanism different from that of antidepressant medications; raising the possibility that prior antidepressant use induces an oppositional tolerance specific to pharmacotherapy but not to psychotherapy.

The cause of increased pharmacodynamic tolerance after repeated antidepressant drugs is unknown. Increased pharmacodynamic tolerance from antidepressants may result from differences in genetic predisposition to non-response to certain drug classes [28–30], although this has not been a universal finding [31–33]. It is also possible that increase in pharmacodynamic tolerance may result from oppositional tolerance whereby persistent use of antidepressant therapy exceeds that which is required for 'normalization' of monoamine receptor sensitivity needed to correct an acute depressive episode [15, 17, 34, 35]. In this model, persistent antidepressant administration results in a supersensitivity of monoamine receptors which not only sets the stage for depressive relapse or recurrence, but also for a diminished antidepressant response during antidepressant re-administration [15, 17].

The oppositional tolerance model posits that repeated and/or prolonged antidepressant administration, either within the current depressive episode or at various times over the course of the entire affective illness, may initiate and sustain one or more biochemical and/or physiological processes that oppose the initial, desired, acute effects of antidepressant drugs via prolonged and excessive receptor or intracellular alterations [15, 17]. For example, some investigators have suggested that this model may account for the gradual loss of antidepressant effectiveness during prolonged antidepressant therapy, a step-wise loss of antidepressant effectiveness with repeated antidepressant administration, as well as an increase in vulnerability to depressive relapse, rapid cycling affective episodes, and an increase in drug-induced adverse events and prolonged discontinuation syndrome (see [15, 17]).

Others have suggested that inadequate antidepressant doses, inadequate plasma drug concentrations, or non-compliance may result in reduced antidepressant effectiveness [15, 36]. However, these conditions do not explain the finding of an increase in pharmacodynamic tolerance over multiple depressive episodes separated by months or years. One account of this phenomenon is that antidepressants specifically alter normal physiological receptor adaptation in a persistent or repetitive fashion over time which manifests as loss of previously effective therapy or step-wise loss of effectiveness over time [15, 17].

Several caveats should be considered when interpreting the current results. For example, we note that step-wise loss of effectiveness during repeated antidepressant trials over time may be different from loss of effectiveness that occurs during continuation therapy in patients who have already responded to antidepressant therapy. The current study was *post hoc* in nature from data derived from a randomized clinical trial. The trial was not specifically powered to test the hypothesis of an association between prior antidepressant use and current fluoxetine response. It is possible that disease heterogeneity or inter-individual differences in response to various antidepressant classes may have influenced fluoxetine response and remission rates. It is also possible that subjects in the current study with poor fluoxetine response had, by chance alone,

more prior exposure to antidepressant trials than fluoxetine responders or remitters, and that our finding represents a statistical artifact. For example, some subjects may have had poor fluoxetine response for reasons other than pharmacodynamic tolerance (e.g., dosage limitations, inadequate plasma fluoxetine levels, or reduced compliance). Although information on the number of prior antidepressant trials was not limited to the current depressive episode, independent verification of prior treatment adequacy and compliance and the extent of response to antidepressant therapy was often limited and could not always be independently verified.

While our current estimate of the loss of fluoxetine effectiveness was not based upon a prospective study design, STAR*D did employ a repetitive treatment design and reported a similar step-wise reduction in response and remission rates with successive antidepressant trials [8–11]. These observations support findings by our group [2–7] and others [12, 14], suggesting the presence of a step-wise loss of effectiveness over the illness course that may occur with repeated antidepressant trials. Most likely this phenomenon is the result of increased pharmacodynamic tolerance produced by down-regulation of monoamine receptor sensitivity from repeated exposure to antidepressant reuptake inhibitors.

In conclusion, the likelihood of increased antidepressant tolerance, with a reduction in effectiveness, should be estimated in individuals with chronic and recurrent forms of affective disorder by obtaining a detailed treatment history. The current findings underscore the importance of identifying individuals who may be most responsive to antidepressant medications, and where alternative therapies (i.e., mood stabilizer or psychotherapy) may be helpful.

Future drug development should also be directed toward identifying putative antidepressants with low likelihood of producing tolerance.

Conflict of interest: *Dr. Amsterdam is not a member of any pharmaceutical industry-sponsored advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company. Dr. Lorenzo-Luaces is not a member of any pharmaceutical industry-sponsored advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company.*

Funding support: *This research was supported by NIMH grant MH060353. Additional support for the preparation of this manuscript was provided by The Jack Warsaw Fund for Research in Biological Psychiatry of the University of Pennsylvania Medical Center. The clinicalTrials.gov identifier for the study is NCT00044616..*

Authors' contributions to the work: *Jay D. Amsterdam designed and performed the original trial from which these data were derived. He wrote and edited the first and subsequent drafts of this manuscript. Lorenzo Lorenzo-Luaces designed the current analysis plan, conducted statistical analyses, and co-drafted and edited the first and subsequent versions of the manuscript.*

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