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Brief report

How treatable is refractory depression?

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ABSTRACT

Introduction: Patients who do not remit following one or more attempts at treatment present a clinical challenge, as well as prolonged suffering and disability. Discouragement is common, so knowledge of likelihood of eventual remission as well as which treatments might ultimately be effective would help patient and clinician alike.
Method: Thirty-one patients with major depression were recruited, 28 beginning study treatment. All had remained significantly depressed following adequate (4 weeks taking ≥ PDR maximum dose) trials on ≥ two antidepressants having different presumed mechanisms. Patients were begun on tranylcypromine to 60 mg/d, were then treated with up to 120 mg/d and then had dextroamphetamine added. Following two week wash-out, patients were then treated with nortriptyline+lithium, and then phenelzine was added. Each successive phase was entered only if remission had not been achieved, and phases could be skipped.
Results: Eighteen of the 28 patients (65%) remitted in one of the five phases of the study, plus 5 additional patients with open post-study treatment (total remitting, 82%). By study phase, Eight of 27 (30%) patients remitted with initial dosing of tranylcypromine up to 60 mg/d, 6/18 (33%) remitted with above PDR dosing of tranylcypromine up to 120 mg/d, and 1/6 (17%) to adding dextroamphetamine. With nortriptyline, 1/10 (10%) remitted with nortriptyline+lithium, and 1/5 (20%) when phenelzine was added. Eighteen of the 28 patients (64%), or 78% of those who remitted, maintained their good benefit for at least six months.
Discussion: The majority of depressed patients refractory to two or more adequately utilized differently acting antidepressant medications can still remit and about half may maintain remission for extended periods. "Refractory depression" appears to be a relative description for many unresponsive depressed patients.[1]

1. Introduction

Likelihood of depressed patients who are refractory to multiple adequate prior treatments subsequently remitting has received little systematic study. After two unsuccessful medication trials in STAR*D, only 14% remitted with a third and 15% with a fourth pharmacologic treatment (Rush et al., 2006). Birkenhäger et al. (2004) similarly reported only 14% of 77 depressed inpatients refractory to tricyclic antidepressant (TCA) or selective serotonin re-uptake inhibitor (SSRI) remitted with monoamine oxidase inhibitor (MAOI). In contradistinction, two studies reported more than half of refractory patients remitted with above PDR recommended dosing of the MAOI, tranylcypromine (Amsterdam and Berwish, 1989; Nolen et al., 1988). Augmenting TCA with lithium has good double-blind evidence (Henninger et al., 1983; Schopf et al., 1989; Joffe et al., 1993) and both augmentation of MAOI with stimulants (Feighner et al., 1985) and combining TCA and MAOI (White and Simpson, 1981; Feighner et al., 1985; McGrath et al., 1994) have anecdotal evidence.

We, therefore, conducted an open pilot study of sequential use of possibly effective treatments to begin addressing whether chances of ultimate remission are slim following two or more ineffective trials with antidepressant medications.

2. Method

Adults, aged 18–65, meeting DSM-IV criteria for major depressive disorder unresponsive to adequate treatment (≥2/3 PDR maximal dose for ≥4 weeks) with two or more standard antidepressant medications having different putative mechanisms of action were recruited. None was psychotic or needed non-study

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Table 1
Dosing Schedule – times dose raises allowed.

Day	Usual dose tranylcypromine	High dose tranylcypromine	Tranylcypromine*+ Dextroamphetamine	Nortriptyline+ Lithium (mg)	Nortriptyline*+Lithium*+ Phenelzine (mg)
1–3	10 mg	70 mg	2.5 mg	25, 600	15
4–7	20 mg	80 mg	5 mg	25, 600	30
8–10	30 mg	90 mg	7.5 mg	50, 900	45
11–14	40 mg	100 mg	10 mg	50, 900	60
15–17	50 mg	110 mg	12.5 mg	**	75
18–21	50	110	15 mg	**	75
22–49***	60 mg	120 mg	15 mg bid	**	90

* Dose maintained at level ended previous phase.
** Dose adjustments according to blood levels, targets: nortriptyline 100–150 ng/mL, lithium 0.8–1.0 mEq/L.
*** or four weeks on maximally tolerated dose.

Table 2
Prior treatments.

Medication class	Ever received (%)	Adequate trial (%)
SSRI	83	72
SNRI	43	37
bupropion	56	50
TCA	53	32
MAOI	26	21
ECT	32	26
Other*	63	47

mean number of prior trials: 7.4 ± 2.9 (range, 3–14).
mean number of adequate trials: 4.3 ± 1.7 (range, 2–9).
mean number of adequate trials with different putative mechanisms: 3.6 ± 1.1 (range, 2–6).
SSRI selective serotonin reuptake inhibitor.
TCA tricyclic antidepressant.
SNRI serotonin-norepinephrine reuptake inhibitor.
MAOI monoamine oxidase inhibitor.
ECT electroconvulsive therapy.
* Other = mirtazapine ($N=6$), nefazodone ($N=3$).

psychotropic medication. Entry and emergent suicide attempt/ideation requiring hospitalization was allowed if study treatment could be initiated/maintained in the hospital.

Treatment occurred in five sequential steps. Shift to the next step occurred only after nonremission was documented following four weeks on maximal prior step dose. Step 1 was usual dose of tranylcypromine (to 60 mg/d), Step 2 high dose tranylcypromine (to 120 mg/d) and Step 3 tranylcypromine plus dextroamphetamine. Patients skipped Step 3 if they refused a stimulant or had a prior history of stimulant abuse. Step 3 (Step 2 if Step 3 ineligible) nonremitters tapered tranylcypromine and dextroamphetamine, and after a two week delay Step 4 treatment began with nortriptyline plus lithium, both titrated to standard blood levels. Inefficacy during Step 4 led to the addition of phenelzine (Step 5). During each step, upward dose titration was slowed or aborted if side effects dictated, the step ending once maximal study dose or maximally tolerated dose was reached and maintained for four weeks. During Steps 3 and 5, prior doses of tranylcypromine (Step 3) and nortriptyline plus lithium (Step 5), respectively, were maintained. See Table 1 for dosing schedules.

Pretreatment, the Structured Clinical Interview for DSM-IV Diagnoses, Patient Version (First et al., 1996), and a modified Antidepressant Treatment History Form (Oquendo et al., 2003) were obtained. At weekly visits, the treating clinician obtained the Hamilton Rating Scale for Depression, 21-item version ($HAMD_{21}$) (Hamilton, 1960) and the Clinical Global Impression (CGI) (Guy, 1976), and patients completed the Beck Depression Inventory (BDI) (Beck et al., 1961). Remission was defined as $HAMD_{21} \leq 7$ maintained for four weeks. Because of the open nature of the study, analyses are descriptive only. The study was approved by the New York State Psychiatric Institute's Institutional Review Board and all patients signed consent to participate with verbal reconsents prior to entry into each Step beyond Step 1. In particular, it was explained at the beginning of Steps 2, 3 and 5 that the protocol use of medications in these ways was outside FDA approved uses and standard practice guidelines. All patients except those in Step 4 followed a strict tyramine-free diet from the start of MAOI until two weeks following last MAOI dose.

3. Results

Twenty-eight patients signed consent. Eighty-nine per cent were Caucasian including 15 women (54%). Mean age was 43 ± 11 years, $HAMD_{21}$ was 20 ± 4, and BDI was 33 ± 11. Most had gone to college (mean years of education = 16 ± 2, range 12–20 years). Few (18%) were currently married, 68% having never married, only 32% were currently employed, and 32% were on disability. Patients had been depressed for 280 ± 205 months (range, 18–636 months) and had received 7 ± 3 (range, 3–14) prior somatic treatments, including 4 ± 2 (range, 2–6) adequate trials having different mechanisms (see Table 2). Five (18%) had a history of bipolar II or bipolar NOS, all were in a current major depressive episode, 29% ($N=8$) had a past history of dysthymia or depression NOS, 43% (12) had atypical and 11% (3) melancholic features. Comorbid disorders included: panic disorder 29% (8), social phobia 21% (6), OCD 11% (3), eating disorder 25% (7), history of alcohol abuse 4% (1) past drug abuse 11% (3), any comorbid anxiety disorder 46% (13).

Step 1 (usual dose tranylcypromine; $N=27$; one patient entering already taking tranylcypromine 80 mg/d entered directly into Step 2). Mean end tranylcypromine dose was 56 ± 12 (range 10–60) and end $HAMD_{17} = 12 \pm 7$ (range, 0–30). Seven (25%) remitted, two (29%) maintaining their remission. Patients remained in Step 1 8.9 ± 2.6 weeks.
Step 2 (high dose tranylcypromine; $N=19$). Two Step 1 nonremitters refused further treatment. Mean end tranylcypromine dose = 105 ± 20 mg/d (range 60–120), end $HAMD_{17}$ was 12 ± 7 (range, 1–22). Six (32%) patients remitted, three (50%) maintaining. Patients remained in Step 2 8.3 ± 3.5 weeks.
Step 3 (tranylcypromine + dextroamphetamine; $N=6$). Six Step 2 nonremitters had prior substance abuse and seven refused so skipped Step 3. Six Step 2 nonremitters entered Step 3 on a mean tranylcypromine dose = 112 ± 10 (range 100–120). Mean dextroamphetamine dose at the end of Step 3 was 20 ± 14 (range, 5–45), and mean end $HAMD_{17} = 15 \pm 7$ (range, 5–24). One patient (17%) remitted and maintained. Patients remained in Step 3 5.6 ± 5.6 weeks.
Step 4 (nortriptyline + lithium; $N=10$). Two patients refused Step 4. Seven patients received both medicines, while three