Protocol, including statistical analysis plan

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A randomized, double-blind, placebo-controlled, parallel-group study
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Corey Goldstein, MD, John Zajecka, MD, Michael Topel, MA, Patricia Meaden, PhD,
Jagannath Devulapally, MD & Ian Mackey, PA-C
Department of Psychiatry
Rush University Medical Center
1700 West Van Buren Street, Fifth Floor
Chicago, Illinois

Phone: 312-942-5592
Fax: 312-942-2177

PROTOCOL

Title of Study: A randomized, double-blind, placebo-controlled, parallel-group study of flexible dose mixed salts amphetamine (5-60 mg) adjunctive to antidepressant therapy among adult outpatients with major depressive disorder responding inadequately to current antidepressant therapy

Authors: Corey Goldstein, MD, John Zajecka, MD, Michael Topel, MA, Patricia Meaden, PhD, Jagannath Devulapally, MD & Ian Mackey, PA-C

University/Hospital Setting for Conduct of Research: Rush University Medical Center, Department of Psychiatry, Chicago, Illinois; and satellite site in Skokie, Illinois

Study Phase: 4

Introduction/Background:

Significance

Despite an array of treatment options, major depression continues to be a prevalent, debilitating illness. An estimated 13 to 14 million American adults experience debilitating depression; it is a more common than asthma, diabetes or angina. In fact, depression is one of the most frequently encountered presentations by primary care physicians (Berman, 2009). Two-thirds of patients who are new to antidepressant medications do not report a timely remission of symptoms, as conventionally defined by a minimally 50% reduction in symptom severity and achievement of an absolute measured score below a specified cut-off level (Fava, 2003; Fava & Davidson, 1996); forty to fifty percent of patients receiving new AD medication fail to experience a response that is timely. The statistic that 10 to 20% of care-seeking depressed patients remain significantly symptomatic after 2 years exacerbates these figures (Scott, 1988). Only about one-third of treated patients experience, whether on mono- or adjunctive-therapy, robust remission of symptoms, and this low rate despite the appearance of a number of new treatments for depression in the last few years (Berman, 2009). The cost to society of so many incompletely remitted patients is high: a study as long ago as 1990 stated the then-current cost of depression in the US as $44 billion annually. And this figure was exclusive of significant out-of-pocket costs to families, estimated then to be $5,000 per worker, per year (Davidson & Meltzer-Brody, 1999). The current cost of unsuccessfully treated depression is estimated at 83 billion dollars annually (Fleurence, 2009). The cost to families and loved ones, and the cost of lost opportunity and life experience for depressed individuals personally is incalculable.

Treatment Refractory Depression

While there may be a lack of consensus in precisely defining criteria for an "incomplete response" to antidepressant therapy (ADT) (e.g., "treatment refractory," "treatment-resistant," "non-responders," "difficult to treat," or "incomplete responders"), it is widely recognized that many patients do not achieve a complete response (remission), and up to 10% of all depressed patients receiving treatment fail treatment completely (Goren, 2001). "Treatment resistance," for our purpose, is defined as the failure of at least one adequate trial of an antidepressant medication (Carvahlo, Machado & Cavalcante, 2008). We note that the associated public health burden referenced above is derived from all patients with continued symptoms, and this includes

those conventionally termed "responders" yet who have not achieved a true remission. Importantly, residual symptoms are associated with an increased risk of relapse (Londen, 1998; Thase, 1992), impaired social and occupational functioning (Judd, 1998; Paykel, 1995; Miller, 1998), and, obviously, chronicity (Judd, 2000). Based on these findings, achieving sustained remission is the commonly accepted "gold-standard" of therapeutic goals (Zajecka, 2003; Thase, 2003).

Again, in spite of the continuing swell in both the number and diversity of pharmaceutical medications with antidepressant mechanisms (Papakostas and Fava, 2005), accumulating data indicates that many patients suffering from major depression have persistent symptoms in spite of treatment efforts. To wit, Corey-Lisle et al (2004) reported that "approximately 22% of patients receiving treatment for depression by their primary-care physicians remitted following 6 months of treatment." Similarly, Rush et al (2004) reported only an "11% remission rate among depressed outpatients" following 12 months of ADT in "one of several public-sector community clinics." In the course of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, Trivedi et al. (2006) followed nearly 3,000 outpatients with MDD who had been prescribed open-label citalopram. The authors reported remission rates of 28-33%. Finally, Petersen et al (2005) studied outpatients with MDD enrolled in "one of two hospital-based, academically-affiliated depression specialty clinics (namely, Massachusetts General Hospital, an affiliate of Harvard Medical School and Rhode Island Hospital, an affiliate of Brown University)," and reported a 20.5-30.7% remission rate among patients receiving a single treatment. To complicate matters further, even among patients achieving remission residual symptoms are common (Nierenberg et al, 1999). These lingering symptoms are associated with reduced adaptive psychosocial functioning (Papakostas et al, 2004a), as well as increased (Paykel et al, 1995) or accelerated (Judd, 1998, 2000) relapse rates. In addition to this burden to society of incomplete symptom remission or relapse, the side-effect burden of many ADs is high. Common AD and atypical antipsychotic medication side effects include weight gain, metabolic syndrome, extra-pyramidal symptoms, sexual dysfunction and somnolence (ibid), and it is axiomatic that high side-effect burden equals low medication compliance.

Augmentation and combination

Augmentation or combination treatment as a treatment strategy, suggested by some authors as preferable to monotherapy as an initial treatment plan is increasingly supported in the literature and in clinical practice. These treatment strategies may increase symptom relief, treatment compliance, and ease side-effect burden (Fava & Rush, 2006). Potential alternative medication strategies in difficult cases include the use of lithium, tricyclic medications, buspirone, combining medications and switching (Fleurence, 2009). STAR*D has shown that augmenting early, rather than waiting for treatment failure, increases the likelihood of remission and decreases the chances of relapse (ibid).

Prompt treatment, especially in the index episode predicts a more robust response. Conversely, delaying augmentation in patients showing resistance to monotherapy has been shown to correlate negatively with complete remission and positively with increased chance of relapse, even if complete remission is achieved (Rush, 2007). There is, however, a lack of consensus among psychiatrists as to what comprises proper, evidence-based treatment for patients with incomplete response, and this is due largely to insufficient data from rigorous studies. Due to the

challenge MDD poses to both clinicians and the patients they treat, and, due to the cost to society itself, creating new, effective treatment strategies for MDD is needed urgently to further elevate the standard of care for depression (Montgomery, 2006).

Switching medications has been shown to be effective treatment strategy in refractory depression, as is augmentation, although, obviously, the quality of patient response to the selected initial medication tends to predict which of the two second-line treatment approaches will be more effective. That said, generally, patients who initially show an incomplete response have shown better improvement with augmentation than that seen with switching (Rush, 2007).

Augmentation Options

The FDA has approved only 2 medications and 1 medicinal food for adjunctive use with ADs in patients failing to show adequate response to AD monotherapy: quetiapine, aripiprazole and L-methylfolate (ibid). This governmental approval is consistent with the findings of the STAR*D study. Significantly, STAR*D references for augmentation, however, did not include antipsychotics, supplements, or stimulant medications. Primarily, data that does exist for stimulant use in treatment of depression supports it as an augmentation rather than as monotherapy (Chiarello & Cole, 1987). (Note: Symbyax, a combination of fluoxetine and olanzapine, has very recently received approval for treatment resistant depression.)

Of these additional approved medications, aripiprazole has been found to be effective in increasing interest and motivation as well as enthusiasm. Aripiprazole does, however, carry a side-effect burden. In a recent acute study of aripiprazole, 18% of subjects experienced akathisia; other common side-effects included headache, somnolence, dizziness, restlessness, insomnia, constipation, diarrhea, nausea, fatigue, blurred vision and upper respiratory infection (Berman, 2009).

The alternative FDA-approved, pharmaceutical, AD-augmenting agent, quetiapine, has been shown to improve depressive symptoms, especially insomnia and anxiety. It does, however, also carry a side-effect burden. Garakani, et al. (2009) found weight change, symptoms of dizziness, and GI symptoms, the last-mentioned being the only side effect to achieve differentiation from placebo. In extended release quetiapine, McIntyre et al. (2009) found sedation, somnolence, EPS, weight gain, and an increase in fasting glucose.

Dopamine and stimulant use in depression

*C*ommon AD medications have focused on 5-hydroxytryptamine (5HT) or norepinephrine (NE) although dopamine (DA) is a key endogenous neurotransmitter implicated in regulating mood, motivation, one's level of interest or pleasure, and other key hallmarks of depression (Dunlop & Nemeroff, 2007). The few randomized controlled trials of stimulants' efficacy available consist largely of acute, uncontrolled data (Orr & Taylor, 2007). There are limited reports in the literature of TCA monotherapy failure being rectified by stimulant augmentation (Wharton, 1991).

A familiar potentiation strategy is that of TCAs via methylphenidate (MPH). Gwitzman (1994) found that MPH speeds the effect of TCA response, especially in the first and second weeks of treatment. Studies of stimulant augmentation of ADT have been conducted, but with mixed

results. Fawcett, et al (1991) found clinically significant results with TRD patients when combining pemoline or dextroamphetamine with MAOIs. SSRIs in combination with MPH or dextroamphetamine have been commonly utilized clinically (Shelton, 2010). Candy et al (2009) reviewed 24 randomized, controlled trials of five psychostimulants using as monotherapy for depression, and found that only 13 of the 24 had "some useable data," and among these, only three demonstrated "oral psychostimulants significantly reduced short-term depressive symptoms in comparison with placebo." These authors characterized the quality of the reviewed studies as generally "low." Conversely, Fawcett, et al. (1991) found that a majority (78%) of study patients had a good response to at least one stimulant plus a monoamine oxidase inhibitor (MAO-I). Significantly, the authors of this study documented the safety of adjunctive stimulant medication in this population.

Similarly, treatment-resistant depression subjects unresponsive to MAOI monotherapy or to MAOI administered with a TCA did respond upon the addition of amphetamine or methylphenidate (Feighner, et al., 1985). It is interesting to note that of the five reviewed stimulants, pemoline is no longer available, and modafinil is not, strictly speaking, a psychostimulant, but rather, may elevate the release of norepinephrine and dopamine from synaptic terminals and elevate hypothalamic histamine levels (Ishizuka, Murakami & Yamatodani, 2008).

There is little research evidence supporting the use of stimulants as augmenting ADs. As of 2007, no randomized controlled trials (RCTs) of stimulant augmentation for TRD existed (Carvahlo, 2007). Stimulant monotherapies currently studied include methylphenidate, methamphetamine, dexamphetamine, pemoline and modafinil (Candy 2009). These studies have shown positive findings for improvement in anergia and fatigue symptoms, with only slight improvement in mood. General mood symptoms as measured by the MADRS did not typically differentiate from placebo. Cited concerns included the short half-life of stimulant medication and the risk of abuse of the medication (Carvahlo, 2008).

MPH has been found to successfully augment citalopram in elderly patients; 8 of 10 patients so treated showed clinically significant improvement by week 8 (Lavretsky & Kumar, 2001). In a subsequent pilot study, Lavretsky et al. found that 5 of 6 patients randomized to active citalopram and MPH achieved remission (HDRS-24 $\leq$ 10) compared with none of those in the CIT plus placebo group (2006). Concordantly, Masand et al. (1998) found in their 7-case series that every patient, previously responding only partially to a 2nd generation AD, achieved a marked improvement, especially in apathy and fatigue, when augmented with a stimulant. Consistent with these findings, Fleurence, et al. (2009) found in their review of TRD augmentation studies that Hamilton and Montgomery-Asperg symptoms do not generally improve with stimulant augmentation, however, CGI scores do improve, as do measures of sleep and energy. Wagner et al (1997) found that 95% of studied patients (male, HIV positive) who completed at least six weeks of treatment reported substantial improvements with regard to both mood and energy at a median dosage of 10 mg per day of dextroamphetamine. Olin and Massand (1996) found that 83% of a group of hospitalized cancer patients achieved some improvement of depressive symptoms when treated with either dextroamphetamine or methylphenidate; 73% showed marked or moderate improvement.

Stimulant augmentation of ADs' particular efficacy
The few rigorous studies of stimulants' efficacy available consist primarily of acute, uncontrolled data (Orr & Taylor, 2007). There are a small number of findings in the literature of TCA monotherapy failure being successfully augmented by stimulant medication (Wharton, 1991).Gwitzman (1994) found that, especially in the first and second weeks of treatment, MPH speeds the effect of TCA response, Fawcett, et al (1991) found clinically significant results with TRD patients when combining pemoline or dextroamphetamine with MAOIs. It is a common clinical practice to use SSRIs in combination with MPH or dextroamphetamine (Shelton, 2010).

In elderly patients, methylphenidate has been found to successfully augment citalopram; 8 of 10 patients so treated showed clinically significant improvement, although improvement did not necessarily occur previous to week 8 (Lavretsky & Kumar, 2001).found that 5 of 6 patients randomized to active citalopram and MPH achieved remission of symptoms (HAM-24 $\leq$ 10) compared with none of those randomized to the CIT plus placebo group so remitting (2006). Concordantly, Masand et al (1998) found in their 7-case series that every patient (previously responding only partially to a 2nd generation AD) achieved a marked improvement, and we note, especially in the symptoms of apathy and fatigue, when augmented with a stimulant.(2009) found in their review of TRD augmentation studies that symptoms rated by the Hamilton and MADRS scales do not generally improve with stimulant augmentation, however, CGI scores do improve, as do measures of sleep and energy.

Selegiline, an MAO inhibitor, through certain of its metabolites (L-amphetamine and L-methamphetamine) is known to increase DA synthesis. Feinberg (2004) reviews the efficacy of augmentation of MAOI ADs with selegiline and proposes the practice may have some clinical utility, including in cases of TRD. The author notes that the availability of transdermal selegiline would decrease the potential for abuse of add-on stimulant medication. Again, further study is recommended by the author.

Ng's 2009 report of his survey of New Zealand psychogeriatricians finds that stimulants are consistently and successfully, if not frequently utilized in that population to augment treatment-resistant cases. He later elaborated (2009) that such stimulant augmentation improved specifically fatigue and apathy, promoting wakefulness, alertness, and possible mood enhancement. In a further elaboration, Ng (2009) explores whether psychostimulant medication may have efficacy among treatment-resistant cases across a broader demographic. The above findings are consistent with this study's assertion that depression is usefully conceptualized as a disorder comprised of a constellation of symptom domains, each domain potentially responding best to a particular treatment strategy.

Larger, higher quality trials are commonly recommended by authors writing on this matter, and stimulant medication is suggested as deserving of serious consideration as a treatment alternative, despite the limited supporting evidence gathered to date (Orr & Taylor, 2007; Parker & Brotchie, 2009). The literature evaluating research on the use of stimulant medications as monotherapy or for adjunctive use have consistently cited the need for larger, randomized-controlled studies of this treatment modality (Candy, 2009; Dunlop & Nemeroff, 2007; Davidson & Meltzer-Brody, 1999; Carvahlo, 2008).

Questions about both the difficulties encountered with patient medication compliance and abuse of stimulants have been raised (Orr & Taylor, 2007). Misuse of stimulant medication is a commonly held concern by prescribing clinicians. Psychostimulant medications "possess significant abuse potential because of their ability to stimulate brain reward system pathways such as [the] mesocorticolimbic dopamine [pathway]…" (Tremblay, 2002). Lessenger and Feinberg (2007) found that, in 2005, prescribed and OTC medications were intentionally misused or used for non-medical purposes by 6.4 million persons 12 years and older during the past month. Of the medication classes examined for abuse, 1.1 million had misused stimulant medications. Among adults 18-25, the monthly misuse of prescription drugs increased from 5.4% to 6.3%. The authors describe stimulant medications as being of "particular concern:" in 2004, there were 7873 American visits to the ER due to non-medical use of stimulant medications.

Masand, et al, (1998) found no evidence in their case series of drug-seeking, tolerance or dependency among their patients augmented with stimulant medication. Further, our group has over 25 years of experience in the use of stimulant medications for affective disorders; we have not seen any evidence for an increased risk of abuse potential.

Chronically depressed individuals may, additionally, show a compensatory up-regulation of D2 receptors. This up-regulation complicates initial administration of stimulant medication as it may account for the "high" some patients experience with stimulants (Dunlop & Nemeroff, 2007). As depressive physiopathology eases through the initial course of treatment, this up-regulation normalizes.

Mechanism of Action

Based on animal studies and other research methods, possible mechanisms of the pathophysiology of depression include reward deficits thought to be caused by deficiencies or dysfunction in DA regulated CNS systems. If the reward threshold is too high, the patient may experience anhedonia, decreased motivation, impaired concentration (Dunlop & Nemeroff, 2007; Cryan, 2003). Diminished DA effect may be caused by impaired presynaptic release, altered intracellular processing, or by a change in the number of post-synaptic receptors. Dopamine operates in the mesocortical (concentration and working memory), mesolimbic (motivation, pleasure, reward), nigrostriatal (motor planning), tuberoinfundibular (sexual behavior), and thalamic regions of the brain. Impairment in these systems may especially manifest as a decreased ability to work for reward and increase in learned helplessness (Dunlop & Nemeroff, 2007).

The pathophysiology of MDD consists of "functional changes in the neurotransmitter and neuroendocrine systems, such as the monoamines and the hypothalamic-pituitary-adrenal axis, as well as functional neuroanatomical changes in the cingulate, insula, amygdala, basal ganglia, caudate, and frontal, prefrontal, parietal, and temporal lobes" Tremblay (2002). The author noted a marked positive correlation between depression severity and "degree of dextroamphetamine [reward] effects." "Patients who were more depressed (Hamilton equals greater than 23) experience a greater degree of rewarding effects, whereas patients with moderate depression did not differentiate from controls (Tremblay, 2002).

It is commonly held that stimulant medications (eg, amphetamine, methylphenidate, pemoline) have mood-elevating effects. Amphetamine, for example, is primarily an indirect-action sympathomimetic agent with certain direct agonist properties, which are achieved through direct neuronal release of DA and NE; blockade of catecholamine reuptake and weak monoamine oxidase inhibition (Biel & Bopp, 1978). Alternatively, methylphenidate is similar, structurally and mechanistically to amphetamine and pemoline is hypothesized to augment catecholamine transmission (Chiarello & Cole, 1987). AMPH designates an *a*-methyl-phenmethyl-amine motif. "J.H. Biel and B.A. Bopp (1978) state the definitive structural features of AMPH as (1) an unsubstituted phenyl ring, (2) a two-carbon side chain between the phenyl ring and nitrogen, (3) an a-methyl group, and (4) a primary amino group" (Sulzer, 2005).

Amphetamine refers to the class of drugs that predominantly releases catecholamines by a non-exocytic mechanism. Amphetamines elevate extra-cellular levels of catecholamines and serotonin. Amphetamines have been utilized by humans via plant availability in the genus *Ephedra* and the tree *Catha Edulis.* B-phenethylamine, phenylethanolamine, tyrosine, and tryptamine are formed in the peripheral nervous systems and the brain. These aromatic amino acid metabolites may modulate behaviors such as excitement and alertness (Sulzer et al, 2005).

There is evidence for multiple sites of action by endogenous and synthetic amphetamines. AMPH has also been suggested to induce CNS dopamine release. AMPH is supposed to act on membrane transporters and so to aid in dopamine synthesis, and modulate monoamine availability in both the cytosol and in synaptic vesicles. and the cytosol, and also to aid in dopamine synthesis. The effect of AMPH on vesicles is unclear. Stimulants generally create dopamine release in the striatum (Sutzer, 2005). Dopamine is thought to play a role in the pathophysiology of depression, either through diminished presynaptic DA release, or through changes in number or function of post-synaptic receptors (Dunlop & Nemeroff, 2007). Amphetamines act as monoamine oxidase inhibitors and have "effects on plasma membrane and vesicular transporters to increase the quantity of biogenic amines available for release by inhibiting [monoamine oxidase]" (Sulzer et al 2005).

Defects in the underlying "brain reward system may underlie specific and core symptoms of depression such as loss of pleasure or interest." The brain reward system consists of "extensive pathways that mediate behavioral components of reward such as pleasure and motivation." Brain reward system studies in humans have pointed to this circuit's involvement in the reward-activities of psychoactive compounds such as of cocaine, nicotine and dextroamphetamine (Tremblay, 2002).

"AMPH has long been noted to enhance dopamine synthesis, and this provides an important role in its action under some conditions." (Sulzer et al 2005). Wharton (1991) found methylphenidate "appears to involve an increase in the blood levels of antidepressants through enzymatic inhibition of the metabolism of imipramine," as does methyl imipramine, which increase is concomitant with clinical improvement.

According to David Mrazek (2010), dopamine transport is modulated by the SLC6A3 gene, the dopamine transporter gene, known as DAT or DAT1. This gene "produces a protein that transfer dopamine from the synapse back to the neuron" (p. 125). This is important because reuptake of

DA back into the neuron switches off DA stimulation in the synapse. Variations in this gene may be implicated in disorders such as "ADHD, binge eating, depression, bipolar disorder, and alcoholism (Mrazek, 2010, p. 125).

Mrazek also addresses the DRD4 DA receptor gene and the D4 DA receptor. This receptor is "located predominantly in the prefrontal cortex" (p. 207). Variations in the density of D4 receptor in the PFC have been implicated in diseases such as Parkinson's and schizophrenia. Mutations in the DRD4 gene have also been implicated in ADHD (2010). For all the limitations in study methodology and other design factors determining study significance, sufficient evidence clearly exists, both clinically and scientifically, supporting the need for further inquiry into to the use of DA modulating (stimulant) medications in mood disorders; specifically, in treatment-resistant depression.

Primary Objective: Generate evidence-based data on the efficacy, safety and tolerability of flexible dose mixed salts amphetamine (MSA) adjunctive to antidepressant therapy (ADT) among adult outpatients with major depressive disorder (MDD) who have responded inadequately to at least 8 weeks of ADT.

Research Hypotheses:

1. Primary outcome: The group treated with MSA adjunctive to ADT will show a greater mean change from baseline to endpoint in total score as compared to the group treated with placebo (PBO) adjunctive to ADT as measured by the
    a. Massachusetts General Hospital Cognitive-Physical Function Questionnaire (MGH-CPFQ)

2. Secondary outcome:
    a. MSA adjunctive to ADT will demonstrate clinically acceptable safety and tolerability, compared to placebo, based on
        i. spontaneously reported adverse events and significant adverse events
        ii. significant changes in blood pressure and pulse
        iii. significant changes in weight
        iv. significant changes in electrocardiogram
        v. significant changes in the Rush Sexual Inventory

    b. The group treated with MSA adjunctive to ADT will show a greater mean change from baseline to endpoint as compared to the group treated with PBO adjunctive to ADT as measured by the change on
        i. MGH-CPFQ individual item analysis
        ii. MADRS scores:
            1. Total score
            2. Subscales
            3. Individual item analysis
            4. Percent of "responders" (≥ 50% reduction in score baseline to endpoint)
            5. Percent reaching "remission" (score of ≤ 10 at endpoint)

c. The group treated with MSA adjunctive to ADT will show statistically significant improvement in core residual symptoms of MDD extant on monotherapy ADT as measured by the
   i. PGI (Patient Impression and Improvement) scales
   ii. Quick Inventory of Depressive Symptomatology-16 (QIDS-16) total score (≤ 6) and subscale
   iii. Clinical Global Impression-Severity (CGI-S); and, Clinical Global Impression-Improvement (CGI-I)
   iv. QIDS total score and subscale

d. The group treated with MSA adjunctive to ADT will show statistically significantly improvement in overall functioning (work, social and cognitive) when compared to the group treated with PBO and ADT as measured by the
   i. Total and individual item scores from the HDRS-17 and -28
   ii. Maier and other subscale scores from the HDRS-17 and -28
   iii. Scale For Assessment Of Negative Symptoms (SANS)
   iv. Health Status Questionnaire, 2nd ed. (HSQ 2.0)
   v. SF-36 Health Survey (SF36)
   vi. Fawcett Experienced Pleasure Index (EPI)
   vii. Endicott Work Productivity Scale (EWPS)
   viii. Sheehan Disability Scale (SDS)
   ix. Fatigue Associated with Symptoms of Depression (FASD)

Study Design: A randomized, double-blind, placebo-controlled, parallel-group study of flexible dose mixed salts amphetamine (5-60 mg) adjunctive to antidepressant therapy among adult outpatients with major depressive disorder responding inadequately to current antidepressant therapy.

Fig. 1: Treatment Groups

	Group 1	Group 2
Phase 1	PBO	MSA
Phase 2	MSA	MSA

Fig. 2: Study Design Overview

Visit	Phase	Weeks on med	Group 1	Group 2	Procedures
V1		Scr			Inclusion/Exclusion
V2		0			Baseline measurement + disp.
V3	I	1	MSA	PBO	Measure effect of 1 week on study med + disp.
V4	I	2	MSA	PBO	Measure effect of 2 weeks on study med + disp.
V5	I	3	MSA	PBO	Measure effect of 3 weeks on study med + disp.
V6	II	4	MSA	MSA	Measure effect of 3 weeks on study med + disp.
V7	II	5	MSA	MSA	Measure effect of 3 weeks on study med + disp.
V8	II	6	MSA	MSA	Measure effect of 3 weeks on study med
V9		(8)			Safety follow-up

The treatment phase of the study consists of 2 phases (21 treatment days per phase). Study Phase 1 will consist of visits 2 (baseline) through 5. Study Phase 2 will consist of visits 6 through 8. There will be a follow-up visit 2 weeks following visit 8. There is a one-week interval between study visits, with a scheduling window of +/- 3 days allowed.

Mixed salts amphetamine is FDA-approved for Attention Deficit-Hyperactivity Disorder (ADHD) and superior in efficacy to placebo; therefore, comorbid ADHD will be statistically controlled as a continuously-variable covariate, but will not be considered an exclusionary condition.

The primary analysis will be a repeated measures analysis of variance using a mixed-effects model (PROC MIXED-MMRM). The primary outcome measure will be the MGH-CPFQ total score at baseline and the MGH-CPFQ total score at the end of the trial. The independent variables will be the study visit, the treatment in the previous phase, and treatment assignment. The variance covariance matrix for the repeated measures will be unspecified.

Enrollment Period: The enrollment period is estimated to be 6 months. The last patient is expected to complete the study by March 31, 2010.

Number of Subjects: 40 subjects will be randomized (20 to each treatment arm). Additional subjects may be consented to allow for screen failures. Subjects who terminate early post-randomization will be replaced only sufficiently to ensure a total number of 24 (12 to each treatment arm) evaluable subjects.

Duration of Subjects' Study Participation: There will be a total of 9 study visits over a period of 9 weeks.

Inclusion Criteria:

1) Male or female outpatients between the ages of 18-70.
2) Subject must meet criteria for single or recurrent, non-psychotic episode of MDD according to DSM-IV-TR diagnosis, as determined by Structured Clinical Inventory of Depressive Symptoms (SCID) and confirmed by assessment of investigator.
3) Current depressive episode must be at least 8 weeks in duration.
4) HDRS-17 score $\geq$ 14 at both the screen and baseline visits.
5) Subject must have been receiving an adequate, stable dose of ADT, based on Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ).
6) Subject must be responding inadequately to his/her current monotherapy ADT in the current major depressive episode (MDE).
7) Subjects must be able to read and understand English and be able to provide written informed consent.
8) Subjects must be considered reliable, able to comply with protocol requirements and understand the risks and benefits, per the investigator's clinical judgment.
9) Female subjects of childbearing potential must agree to use adequate form of birth control throughout the course of the study.

Exclusion Criteria:

1) Inadequate response during the current episode to more than 3 adequate trials of an ADT, as defined by the MGH-ATRQ.
2) Psychiatric hospitalization within the last 6 months.
3) Presence of cognitive disorder(s), bipolar disorder, Axis II pathology or other condition that investigator believes would interfere with participation in the study.
4) Substance use disorder, current (as defined by DSM-IV-TR SCID) or positive results on urine drug screen or laboratory blood tests.
5) Risk to self or others.
6) The presence of any medical condition, current or past, stable or unstable, that contraindicates the use of antidepressant medication or mixed amphetamine salts medication as determined by clinician's judgment.
7) Clinically significant abnormal findings on physical exam, EKG or laboratory tests; current unstable, untreated hypertension in the opinion of the investigator; history of cerebrovascular accident (CVA) or seizure disorder (other than febrile childhood seizure).
8) Allergies and/or adverse drug reactions to MSA.
9) Failure to respond to an adequate trial of MSA adjunctive to ADT in the current episode.
10) Subjects taking narcotics, herbal/homeopathic remedies and/or other substance with psychotropic activity, based upon clinical judgment of study investigator.
11) Pregnant or breastfeeding women.

Study Procedures: Figure 3 shows study procedures to be performed at each visit. No study procedures will be performed until a subject signs the informed consent document.

Screen visit (Visit 1): Medical and psychiatric history will be taken, a physical examination and vital signs will be performed and lab tests done. Lab tests include CBC, CMP, urine drug screen and urine pregnancy test for females of childbearing potential. If a subject has had the required lab tests performed within the past 3 months and can produce the results, lab procedures may be waived at the screening visit for that patient (except urine pregnancy test). The HDRS-17 score upon screening will be used to determine entry eligibility (see inclusion criteria). Beyond the patient's verbal report, we will attempt to obtain medical records (e.g., previous clinician or pharmacy records) to document adequate dose and duration of previous/current ADT.

Study Phase 1

Baseline visit (Visit 2): Screened and eligible subjects will return one week after the screening visit. At this visit (provided entry criteria continue to be met) subjects will be randomized in double-blind fashion to one of two treatment groups:

- Group 1: MSA during both phases; or
- Group 2: PBO during Phase 1 followed by MSA during phase 2

Study drug will be dispensed to the subject in sufficient quantity to last until the next study visit (7 days +/- 3).

Study visits 3-5: Following the baseline visit, subjects will return at one-week intervals for study visits 3-5. Study procedures to be performed are reflected in Figure 3. Phase 2 study drug is dispensed at study visit 5.

Study visits 6-8: Subjects will return at one-week intervals for study visits 6-8. Study procedures to be performed are reflected in Figure 3. At visit 8, all subjects will receive instructions for tapering the dose of the MSA to avoid potential difficulties from abrupt discontinuation of the study drug.

Study visit 9: Subjects will return two weeks following visit 8 for a safety follow-up check. Procedures to be performed are reflected in Figure 3.

If a subject withdraws or is terminated early from the study, visit 9 procedures will be performed at the final study visit.

All concomitant medications taken during the study will be recorded in the case report form, along with dosage information and start and stop dates. Subjects requiring excluded drugs will be discontinued from the study. Medication management and clinical ratings will be performed by the study clinicians.

Subjects who complete the trial will be offered referrals to qualified physicians for the purposes of continued care. At the conclusion of Visit 8, study blind will be removed by an unblinded study staff member for facilitation of ongoing treatment by patient's selected follow-up care provider. At Visit 8, study subjects will be provided a one-month prescription for the dose of MSA they are currently prescribed in the study to ease transition to their follow-up care physician.

At the end of the study, subjects will be followed for up to three months while an appointment can be secured with their original treatment provider or with one referred by the research center.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Based upon clinical judgment and ascertained between clinician and patient, study drug will be dosed as follows: The total daily dosage of study drug will be 5-60 mg, supplied in 5 and 10 mg tablets of MSA or matching PBO.

Total daily dosing of the concurrent ADT will be as follows: escitalopram 10-40 mg; fluoxetine 20-80 mg; paroxetine CR 25-100 mg (paroxetine 20-80 mg may be substituted if paroxetine CR is not available); sertraline 100-400 mg; venlafaxine XR 150-600 mg; desvenlafaxine 50-200mg; citalopram 20-80 mg; or duloxetine 60-180 mg; bupropion 150-450 mg; mirtazapine 15-45 mg, tricyclics (standard dosing, individually per label instructions).

The dose of MSA begins at 5mg BID. MSA dose range will be 5mg-20mg BID or TID, not to exceed 60mg per day in addition to the stable dose of ongoing ADT. Each study medication tablet will be 5 or 10 mg of MSA or PBO. Upward titration will be based upon physician's clinical judgment and confirmed by patient's consent.

Subjects unable to tolerate the study medications will be withdrawn from the study. Every effort will be made to encourage patients to comply with this dosage regimen and to take all study medications and their ongoing concomitant ADT as instructed. All patients will be instructed to return any excess medication at each visit. A pill count will be done to corroborate the study drug record. Protocol violation will be defined as less than 80% compliance by pill count.

MSA doses will be custom-tapered per physician's discretion starting at visit 8.

The study medication packager will use a block randomization scheme to distribute the kits within each box/block.

Risk/Safety Information: The principal investigator and subinvestigators are responsible for monitoring the safety of the subjects who have entered this study and for alerting the IRB of any event that meets IRB reporting criteria. The investigator is also responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the subject to discontinue before completing the study. The subject should be followed until the event resolves or is explained. Frequency of follow-up is left to the discretion of the investigator.

Monitoring and Reporting of Adverse Events and Serious Adverse Events:

Adverse Events:
All observed or volunteered adverse events, regardless of suspected causal relationship to study drug, will be recorded on the case report form and reported to the IRB if reporting criteria are met.

Serious and/or Unexpected Adverse Events:
Study site personnel will report to the IRB any serious and/or unexpected adverse event following IRB reporting guidelines. A serious adverse event is any adverse experience that results in one of the following outcomes, or is significant for any other reason:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Severe or permanent disability
- Cancer
- Congenital anomaly

Serious adverse events occurring after a subject is discontinued from the study will not be reported unless the investigator feels that the event may have been caused by the study drug or a protocol procedure.

Unblinding Procedure
Unblinding may be performed only by unblinded site personnel, under two conditions:

- If necessary for treatment of the subject in the event of a medical emergency
- Upon a subject's completion of the study (visit 8), in order to facilitate continuation of care by a non-study clinician

Monitoring of Study/Oversight:
Study staff will monitor source data and case report forms by regular internal monitoring. .

IRB Review/Ethical Conduct of Study:
IRB Review: Prior to enrolling any subjects, documentation will be obtained that the study protocol and informed consent form have been approved by the Rush University Medical Center Institutional Review Board. Any change in the protocol or informed consent form will require prior written approval except to prevent injury or risk to a subject.

Regulatory Considerations: This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

Informed Consent: The informed consent document, in conjunction with verbal discussion of the protocol, will be used to explain the study, including the risks and benefits, to the subject in simple terms before the subject is entered into the study. The investigator is responsible to see that informed consent is obtained from each subject and to obtain the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to any changes made to a subject's medical treatment plan for the purpose of study participation. The original signed consent form will be retained by the investigator.

Confidentiality:
All information collected about subjects for the purposes of this study will be treated as confidential to the extent allowed by law. The information obtained while subjects are enrolled in this study, including all study-related hospital and office records, will be made available to the study doctor, Bristol-Myers Squibb, the Institutional Review Board and other regulatory agencies, including the United States Food and Drug Administration (U.S. FDA).

Intended Use of Data:
The results of this research project may be presented at meetings or in publications, but the identity of subjects will not be disclosed in such presentations.

Statistical Analysis:
Study Assessments and Primary Endpoints: The difference in absolute change in score from baseline to endpoint in the MGH-CPFQ between the MSA and the PBO groups is the primary endpoint. Key secondary endpoints will be difference in absolute change from baseline in MADRS score between MSA and PBO, difference in remission rates (MADRS < 11) between MSA and PBO, the change from baseline in total score at endpoint of MGH-CPFQ item analysis, difference in change scores on the CGI-S, CGI-I and QIDS. Safety outcome measures: adverse events, physical examinations, vital signs; blood pressure, orthostatic; EKG; Rush Sexual Inventory (RSI).

Statistical Methods: The randomized sample includes all patients who are randomized. The Safety sample will include those randomized patients who received at least one dose of double-blind study medication as indicated on the dosing record. The efficacy sample will include those patients in the safety sample who have at least one efficacy evaluation post-randomization. The last observation carried forward (LOCF) data set includes data recorded at a given visit after randomization, or, if no observation is recorded at that visit, data carried forward from the previous postrandomization visit. The LOCF data set is primary, and analysis of the observed case data set also will be conducted.

The primary analysis will compare pooled MGH-CPFQ response rates between PBO and MSA and PBO non-responders. Differences in response rates will be compared using the CMH General Association Test. Descriptive statistics on non-primary groups will be conducted.

This study seeks to estimate the strength of any statistically significant relationship, or effect size, in addition to statistical significance of found treatment effects.

Secondary Endpoints Analysis: Differences in remission (defined as an endpoint MADRS score <11) rates will be compared using the CMH General Association Test. Logistic regression analysis will be performed to explore the relationship between response and patients' demographics and prognostic variables including baseline QIDS score, gender, site, and age, etc. Similar analyses will be performed for remission.

Fig. 3: Study Procedures Table

			Treatment period 1			Treatment period 2			
Study Visit	**V1 Screen**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9 F/UP**
End of Week	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**
Day	**-7**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**
Informed consent	X								
Demographic data	X								
Medical and psychiatric history	X	X							
SCID	X								
Physical exam	X								
Vital signs and weight	X	X	X	X	X	X	X	X	X
EKG	X								X
Lab tests*, urine pregnancy test** and urine drug screen	X								X
MGH-ATRQ	X								
Inclusion/exclusion criteria	X	X							
Randomization		X							
Expectation ratings		X							
Clinician-completed surveys:									
HDRS (17- and 28-item)	X	X						X	
MADRS		X	X	X	X	X	X	X	
CGI-S	X	X							
CGI-I			X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X
Patient-completed surveys:									
MGH-CPFQ	X	X	X	X	X	X	X	X	
EWPS	X	X	X	X	X	X	X	X	
Fawcett EPI	X	X	X	X	X	X	X	X	
FASD	X	X	X	X	X	X	X	X	
HSQ 2.0	X	X	X	X	X	X	X	X	
PGI-S	X	X							
PGI-I			X	X	X	X	X	X	
RSI	X	X	X	X	X	X	X	X	
QIDS-16	X	X	X	X	X	X	X	X	
SANS	X	X	X	X	X	X	X	X	
SDS	X	X	X	X	X	X	X	X	
SF-36	X	X	X	X	X	X	X	X	
Study drug dispensed		X	X	X	X	X	X	X	
Study drug accountability			X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

*Including CBC and CMP. If patient can produce lab results for CBC and CMP performed within the past 3 months, screening procedures may be waived.
**For females of childbearing potential

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