USING WHAT WE HAVE: COMBINING MEDICATIONS TO ACHIEVE REMISSION

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Abstract

This paper seeks to teach clinical principles in the use of polypharmacy in psychiatric practice. Using major depressive disorder, authors discuss clinical practice techniques and thoroughly review the existing literature regarding the polypharmacy of treatment resistant depression. Readers are expected to be able to utilize information directly in clinical practice.

Key Words: polypharmacy, major depressive disorder, resistant depression, refractory depression treatment resistant, psychiatric practice

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Introduction

This paper will use major depressive disorder (MDD) as an example of a psychiatric disorder which has a wealth of treatment options available with varying amounts of evidence base to support their use. The FDA considers all antidepressants to be equally efficacious, as regulatory studies all show similar effect sizes but differing levels of tolerability. Practicing clinicians know that each antidepressant possesses certain clinical attributes which may help one patient moreso than the next. This paper may serve as a model for practicing psychopharmacologists and for those who want to excel in the future as remarkable breakthrough psychotropics may not be on the horizon.

The *first* rule is to follow FDA-level approvals and to practice monotherapy whenever possible. The *second* is to know and follow the evidence-based literature outside of regulatory studies and approvals, especially when using off-label or more esoteric combination therapies. *Thirdly*, when these two rules have sparse support, a clinician should fall back on theoretical applications of known psychotropics based on the particular drug's mechanism of action (Stahl et al. 2008). For example, understanding that MDD may evolve from a deficiency in available monoamine neurotransmitters, an excess of their receptors, or poor communication from one neuroanatomical area and another, clinicians may elect drugs intended to alter these abnormalities to raise neurotransmitter levels, downregulate receptors, etc. This means that psychopharmacologists must memorize FDA approvals, be generally aware of the current literature, and memorize how each antidepressant works in the brain, and how manipulating certain transmitters and receptors may improve target psychiatric symptoms. This article will review the FDA approvals in regards to treating resistant depression with augmentation-combination strategies, the available data supporting lesser-known treatments, and finally, in theory, how these augmentations work mechanistically to treat MDD as a guide when evidence is lacking. This three-rule approach can be followed for any disorder and should provide a high standard of care, which is medico-legally safe, and facilitate an advanced level of psychopharmacological practice. For each pharmacological agent, approvals, off-label data, and mechanistic theory will be discussed in a brief review article manner.

To begin, similar to any other medical illness, depression should be treated to full *remission,* which

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describes a symptom-free recovery. Remission has now become the standard of care for treating individuals with major depressive disorder (MDD), and should be the goal of treatment. This includes both the patient who responds partially in the first episode, and the patient who may have failed to respond to multiple treatments. Unfortunately, up to 50% of patients who "respond" to their antidepressant treatment fail to fully "remit" (Nierenberg et al. 1999). Data from long-term clinical trials of antidepressant response have estimated that approximately two-thirds of patients fail to achieve a full remission (Kupfer and Spiker 1981). More recent findings from the National Institute of Mental Health's Sequenced Treatment Alternatives to Relieve Depression (STAR*D), suggest that in a community sample of patients with depression, approximately 40% of patients failed to "respond" to an adequate trial of a selective serotonin reuptake inhibitor (SSRI) and over 65% failed to achieve remission (Trivedi et al. 2006). This study went on to show that, even when patients were given a chance to switch antidepressants or augment their treatment to a set sequence of treatment alternatives, they achieved only modest improvement of response or remission and, further, showed high rates of residual symptoms (Rush et al. 2006, Trivedi et al. 2006). Furthermore, acute and long-term studies show that high rates of "residual symptoms" remain, or persist, even after treatment of a depressive episode (Nierenberg et al. 1999, Weissman et al. 1978); these residual emotional or physical symptoms of depression significantly increase the risk of relapse and recurrence (Paykel 1995). In addition to increased risk of relapse and recurrence, there are several other possible consequences of failing to achieve remission, including continued psychosocial impairments, increased use of medical services, potentially worsened prognosis of any comorbid medical/psychiatric illnesses, ongoing risk of suicide and at least the theoretical possibility of the patient becoming "treatment resistant" (Thase 1999, Hirchfeld et al. 1997).

In the last several decades, an abundance of pharmacological, psychological and somatic treatment options for the effective treatment of depression have been introduced. There is a growing literature on both the acute and long-term efficacy of these treatments used either alone or in combination. One of the common themes is the importance of treating the index episode of MDD as aggressively as possible to achieve remission and continue to monitor so as to prevent relapse and recurrence. Index episode remission remains among the strongest predictors of whether a patient will avoid subsequent relapse, and do well in the long term (Hirchfeld et al. 1997). The American College of Neuropsychopharmacology Task Force recommended that "full remission" be defined as an absence of both sad mood (anhedonia) and reduced interest (avolition) for at least three consecutive weeks, in addition to the presence of fewer than four of the seven remaining Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition symptoms of MDD (Rush et al. 2006). In clinical research, one of the accepted definitions of remission is a Hamilton Depression Rating Scale (HDRS-17) score of ≤ 7 (Thase and Ninan 2002, Depression Panel No. 5, Dunner 2005). "Response", alternatively, comprises having a minimum 50% decrease from baseline in the total HDRS-17 score (Thase and Nina 2002, Depression Panel No. 5, Dunner 2005). In clinical practice, patients are said to be in remission when they are virtually asymptomatic and, over time, have a return of psychosocial functioning to that of their premorbid state (Thase and Nina 2002, Depression Panel No. 5, Dunner 2005).

The Systematic Treatment Optimization Program for Early Mania (STOP-EM) project findings (2009) note that the reduction of mood symptoms to a subsyndromal level may mask the lack of return to full social and occupational function levels and thus be response or remission in name only (Kauer et al. 2009).

This opening manuscript will be the longest for a few reasons. First, it has the most evidence-base to cover. Second, it is clear from some of the references noted above that remission is the standard-of-care in treating MDD, but is infrequently achieved via monotherapy and, thus, complex polypharmacy is often needed for remission. Currently, practicing psychopharmacologists must be up-to-date on the evidence supporting their clinical practices. Third, as there appear to be no clear blockbuster monotherapy agents for MDD, or other psychiatric disorders, in the immediate research pipeline, the psychopharmacologist of the future must become comfortable with ever-more complicated polypharmacy, possibly combining two or more augmenting agents simultaneously to produce a better chance of remission. MDD has, arguably, the greatest volume of useful data about combining medications to achieve better outcomes of any psychiatric disorder. Our goal is for the reader to obtain a better sense of why combining medications is important, an awareness of the current literature regarding combination strategies, and some ideas as to what is coming in the future.

Strategies to achieve and sustain remission

First, the clinician must always consider the risk/benefit ratio of specific treatment strategies to be tailored to the individual patient. Educating patients that the goal of treatment is complete symptom remission is a vital preparatory step, in addition to confirming diagnosis and comorbidities. It is also important to ensure adequate dosage and duration of each specific treatment used. Inadequate dosing or duration mistakenly construed as a "therapeutic dose" is a common error made in what may appear to be cases of treatment failure. Maximizing the dose of a primary antidepressant should always be considered, even for those antidepressants that have not been shown to have a dose-response effect. Medications such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and the SNRI, venlafaxine, are examples of medications that may have a modest dose-response effect in some patients, yet maximizing the dose of any particular antidepressant should be considered provided as such dose increases do not risk tolerability and/or safety. Antidepressant dosages in some patients may be safely increased to the equivalent of 500 mg/day of imipramine (Janicak et al. 2001, Schatberg and Nemeroff in press, Zajecka and Fawcett 1991). In the case of TCAs, monitoring plasma levels of the

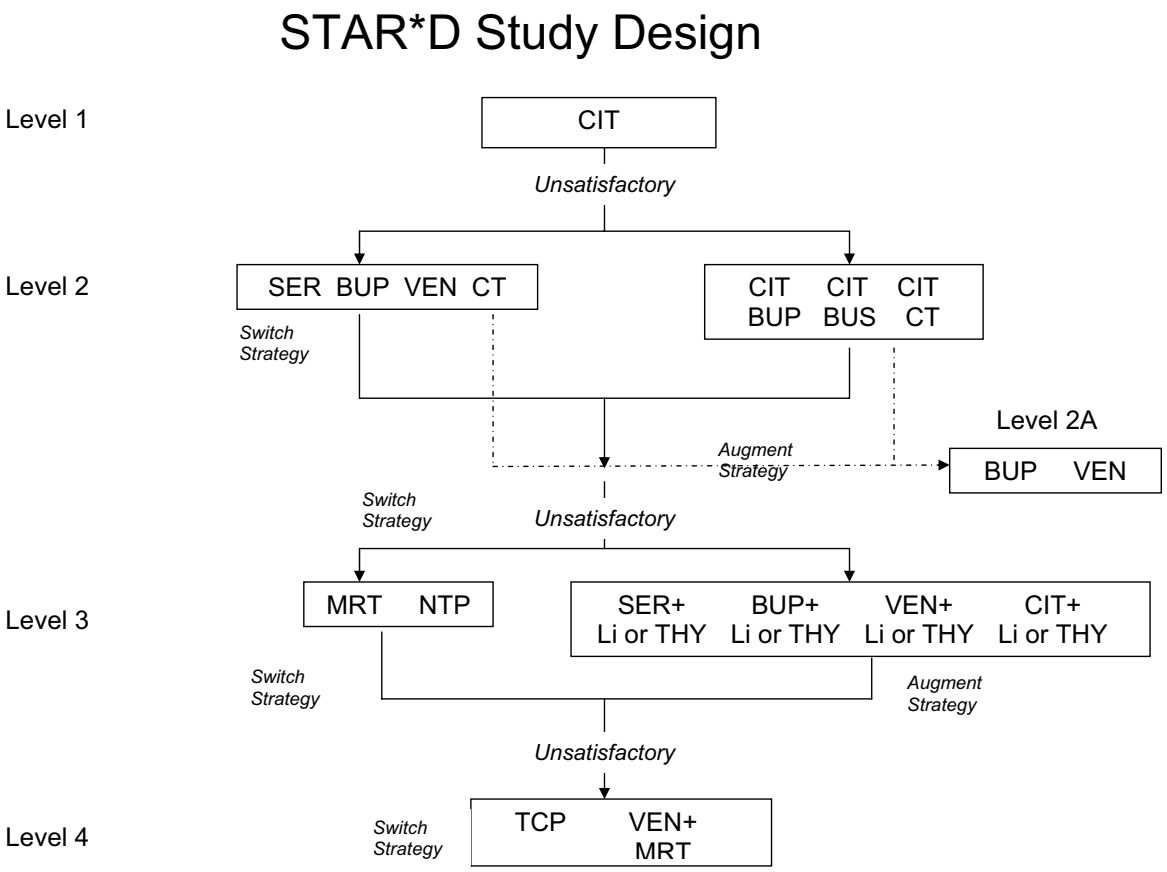
antidepressant or conducting an electrocardiogram to ensure cardiac safety for higher doses may be advisable. While some patients may respond to treatment within the two to three weeks of administration, others may not show a response for 12 to 16 weeks, and full response may not be evident until this latter time. Tolerability and safety issues are paramount in treating all depressed patients, whether using monotherapy or combination treatments. The clinician must remain cognizant of these issues over time because patients may develop comorbid medical illnesses, or other factors may emerge relative to safety and tolerability of a particular treatment. Additionally, clinicians must remain aware of problems with adherence to treatment; it is among the more common causes for failure to achieve and sustain symptom remission.

If monotherapy with a particular medication is not effective, the clinician should then consider one of several strategies, including switching the antidepressant, combining antidepressants, or augmenting the antidepressant with another somatic/pharmacological treatment. The sequence of switching, adjunctive treatment or combination still requires tailoring to the individual patient and her symptoms. The field is just beginning to recognize the importance of testing empirical, evidence-based strategies to guide clinicians. However, even these studies often have their own limitations, as the efforts to obtain data for evidence-based treatments are commonly associated with at least some methodological restrictions. The STAR*D outcome provided clinicians and patients a selection of switch/adjunctive treatment/combination strategies (see **figure 1**), however, these treatment options were limited by several factors, including the level of treatment at which the patient still failed to remit, maximal dose restrictions, and other variables that may have interfered with symptom remission (Trivedi et al. 2006). Therefore, evidence-based treatments should be considered as no more than a guide when selecting a treatment strategy.

Additional considerations include psychotherapeutic interventions and somatic treatments including electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), phototherapy and even "investigational treatments" (**figure 2**) which are covered later in this special issue.

Bauer et al. (2009) and other authors have suggested that algorithm-guided treatment strategies produce better outcomes than a non-structured

Figure 1



CIT=citalopram. SER=sertraline. BUP=bupropion. VEN=venlafaxine. CT=cognitive therapy. BUS=buspirone. MRT=mirtazapine. NTP=nortriptyline. Li=lithium. THY=thyroid hormone. TCP=tranylcypromine.

Rush AJ et al. *Control Clin Trials.* 2004;25:119-142.

Figure 2. *Antidepressant Augmentation*

L-methylfolate	Anticonvulsants
Lithium	lamotrigine
Thyroid hormone	carbamazepine
Buspirone	divalproex acid
Stimulants	gabapentin
amphetamine	Other agents
methylphenidate	SAMe
Atypical antipsychotics	atomoxetine
Benzodiazepines	buprenorphine
Beta-blockers	ketamine
pindolol	riluzole
propranolol	tramadol
Modafinil	dopamine agonists
Steroid hormones	Other somatic treatments
estrogen	ECT
testosterone	VNS
	rTMS
	phototherapy
	Empirical psychotherapies
	CBT
	IPT
	CBASP

Adapted from Zajecka J, Goldstein C, Barowski J. Combining Drug Treatments to Achieve Remission. In: Schwartz TL, Petersen T, eds. *Handbook of Treating Depression/Depression: Treatment Strategies and Management.* New York, NY:Taylor & Francis Group; 161-200, 2006

approach, and recommend a "systematic, stepwise, measurement-based approach" as comprising the gold-standard of care for mood-disordered patients.

Blier et al. (2010) reported that in a RCT of fluoxetine monotherapy or mirtazapine in combination with fluoxetine, venlafaxine, or bupropion, subjects randomized to combination therapy had significantly greater remission rates on the HDRS-17 (score = 7) and remitted at approximately twice the rate of patients treated with fluoxetine alone.

The decision to switch, combine, or augment an antidepressant when initial remission is not achieved

Before making a decision to switch, combine or augment, it is imperative to ensure that the dose of the initial antidepressant has been maximized for an adequate duration of time, at least four to six weeks of an adequate dose. Factors such as suicidality, psychotic symptoms, persistent anxiety or severity of the underlying depression are examples where combining or augmenting may be required at an earlier time. The clinician should remain aware of the current literature in regard to combining or augmenting antidepressants in specific patient populations, and consider the methodology of relevant, published studies in terms of extrapolating such strategies to their own clinical practice. It is helpful to refer to published literature when using specific strategies that are complex, aggressive, or clinically risky, and should be documented in the patient's chart, including obtaining informed consent from the patient. Clinicians should consider the patient's ability to meet the ongoing cost of treatment, the potential for drug interactions, likelihood of adherence diminishing with multiple medications, the rapidity of response, the type of symptoms that the patient continues to present with, family history, patient's own history and the current degree of symptomology.

Our group finds that, when a patient has less than 25% improvement following initial monotherapy, we are more likely to consider switching the antidepressant outright. The clinician can consider combining two antidepressants as long as there are minimal issues with safety or tolerability. If the patient remits in the process of the switch during this "bridging" of antidepressants, one may choose to continue the patient on the combination. For the patient who shows a far greater, but incomplete, response to a particular antidepressant, the clinician may augment that antidepressant with

another pharmacological agent to "enhance" the primary antidepressant effect, rather than risking switching. Finally, for those patients who fall between 25-50% improvement, the decision for switching versus augmenting the primary antidepressant properly takes into account the factors mentioned above, supplemented with questions such as: Is this the first treatment the patient failed? Has the patient has failed multiple trials of several classes of antidepressants? How does the patient feel about the strategy? A higher degree of severity, chronicity, and history of failed treatments would likely lead to combining agents instead of switching monotherapies.

There are a number of practical issues to consider when augmenting or combining antidepressants. It is important to tailor the choice of the treatment to the symptoms. It is also important to consider "synergistic" pharmacological profiles. For example, if the individual is on a SSRI, adding a noradrenergic or dopaminergic agent may be warranted (atomoxetine, methylphenidate, modafinil, pramipexole, bupropion). For depressed patients who have comorbid illnesses that contribute to the underlying residual symptomology, using pharmacological strategies to target those comorbid symptoms may be warranted. For example, for attention deficit disorder, adding a stimulant or atomoxetine; for obsessive-compulsive symptoms, premenstrual dysphoric disorder symptoms or eating disorders, the use of an SSRI may be warranted; for anxiety disorders, using buspirone, benzodiazepines or even atypical antipsychotics may be considered; and, for bipolar disorders, the use of lithium, lamotrigine, carbamazepine, divalproex sodium or atypical antipsychotics may be considered.

Side effects from the primary antidepressant may also guide a clinician to choose a particular pharmacological strategy. For example, a patient who may be suffering sexual side effects and continues to have depressive symptoms may benefit from adding bupropion or a stimulant. Another example is the patient who may be showing a partial antidepressant response, but has symptoms of "asthenia" or "tachyphylaxis" (apathy, fatigue, blunted affect, etc.) may be helped by adding a stimulant, bupropion, atomoxetine, modafinil, or an atypical antipsychotic. Patients with insomnia may require a hypnotic agent; those with agitation an anxiolytic.

In sum, it is imperative that clinicians take into consideration not only the issue of efficacy, but also an awareness of drug interactions, safety, tolerability, cost, patient preference and adherence issues. Of note, a 'win-win' scenario may occur when a clinician adds two medications to enhance efficacy and achieves a resultant decrease in adverse effects, as medications may treat each other's side effects, as well (i.e., bupropion may add antidepressant efficacy and lower sexual side effects when added to a pre-existing SSRI). The ultimate goal should be to boost efficacy and improve tolerability and adherence.

Documentation during management of combination strategies

For complex polypharmacy, more energy must go into documenting this decision process. It is important for clinicians to keep written records of past and current treatment trials (including doses, duration of each dose, tolerability and efficacy) available at all times. Our group finds it helpful for patients to use some form of life charting technique to ascertain the level of subjective and objective improvement that the patient experiences, as well as to serve as an additional tool to show patterns of response, adherence and other potential factors that may impact outcome (e.g., menstrual cycle, substance use and other factors). It is important to obtain verbal informed consent before all interventions, especially when using combination strategies that are not Food and Drug Administration (FDA) approved (i.e., "off-label"). This informed consent should describe the risk and benefit to the patient, explaining in detail the non-approved status of these combinations and their side effects. It is important to invite the patient to ask questions, and to involve the patient's significant others whenever possible.

When there is an absence of findings in the literature, clinicians may rely on theoretical ideas of pharmacodynamics, central nervous system physiology, and clinical utility, which suggest that certain deficiencies in specific neurotransmitter systems or receptors may be the underlying, cause of specific depressive symptoms. For example, a MDD patient who remains fatigued and unable to concentrate may preferentially benefit from the use of a drug that enhances noradrenergic activity. Medical records should note a lack of data from the literature and also note the scientific thinking behind the choice of medication(s) used.

We now conclude this brief overview of some principles of complex polypharmacy; the authors will next provide a review regarding the evidence-base for polpypharmacological medication management of MDD. The concept again suggests that clinicians will likely not find a cure-all monotherapy for all of depression (or any other primary psychiatric disorder) and that clinicians' effective practice will likely benefit from an embrace of the use of polypharmacy strategies to gain the targeted "full remission" goal for a majority of their patients.

Adjunctive medications for MDD

L-methylfolate, methyltetrafolate (MTHF)

Using MDD, the authors will review the evidence regarding polypharmacy of MDD. It may be prudent to start with a full discussion about folate, and moreso, methylfolate, being one of the newest medications approved by the FDA for depression. Methylfolate (L-methylfolate, methyltetrafolate [MTHF]) now has an indication as an adjunct to boost initial antidepressant therapy efficacy. MTHF (Deplin – PamLab) recently received an indication as a "medical food" for MDD that has not fully responded or may not fully respond to initial antidepressant therapy. It is available only by prescription. MTHF is the metabolite of folate, which most readily crosses the blood-brain barrier. The current indication (per label) for adjunctive treatment of depression is for the subtype associated with low serum

folate or red blood cell (RBC) folate. Limited data suggests that low RBC folate predicts low MTHF CNS levels (Obeid et al. 2007), however, further data is needed to clarify whether low RBC level is a sensitive predictor of response to MTHF adjunctive treatment for MDD (Bottiglieri 2005, Fava et al. 1997, Bottiglieri et al. 2000).

The theoretical mechanism of MTHF is to "correct" one of many causes of low CNS MTHF that may be the primary or secondary cause of the depressive symptoms. This is consistent with the monoamine/catecholamine hypothesis of depression and genetic factors in some subtypes of depression. Other authors have postulated that l-methylfolate is a key precursor in the cellular metabolic one-carbon cycle, and that facilitating this system allows for more monoamine neurotransmitter to be formed. This increased availability gives the initial antidepressant monotherapy added supply to manipulate in order to facilitate a reduction in MDD symptoms (Lever et al. 2006, Papakostas et al. 2005 and 2000, Tolmunen et al. 2003, Papakostas et al. 2005, Wu and Pardridge 1999, Spector and Lorenzo 1975, Ruck et al. 1980, Wang et al. 1992, Stahl 2007). Further, MTHF combines with the amino acid homocysteine and with vitamin B_{12} to produce S-adenosyl-L-methionine (SAMe), an essential methyl donor group for synthesis of dopamine, norepinephrine, and serotonin (Bottiglieri et al. 1992, Kaufman 1991, Hamon et al. 1986, Mann and Hill 1983, Sontag et al. 2007) – further boosting available monoamines.

Several trials with monotherapy folate (not l-methylfolate) have demonstrated it to be effective and well tolerated, although the most efficacious dose (40-90 mg/d) and form of folate remain unclear (Guaraldi et al. 1993, DiPalma et al. 1994, Passeri et al. 1993, Coppen and Bailey 2000). Regarding MTHF, Godfrey et al. reported on folate-deficient patients with MDD who were given 15 mg/day of MTHF in addition to psychotropic treatment (1990). These patients experienced a greater reduction of symptoms compared with patients receiving a placebo adjunctive treatment. Alpert et al. (2002) utilized adjunctive treatment with 15 to 30 mg/day of leucovorin (a form of folinic acid that is converted into MTHF) with the resultant sample experiencing a significant reduction in symptoms. Another study reported folate-adjunctive treatment enhanced lithium response in patients being treated for bipolar and unipolar depression (Godfrey et al. 1990).

A poor response to SSRI medication may suggest a likely candidate for 5-MTHF adjunctive treatment, given its benign side effect profile. It is likely one of the safest augmentation strategies (Miller 2008, Stahl 2008). Given the indication as a prescription medical food adjunctive treatment, MTHF can be considered as "first-line" among choices for adjunctive treatment at any stage of treatment.

A 2009 review found the choice of a specific folate form may be informed by patient characteristics such as the presence of a genetic polymorphism, patient use of certain medications or use of alcohol, the presence of residual depressive symptoms (partial-responder) and patient age. The 5-MTHF formulation showed efficacy adjunctively or as monotherapy for patients with either normal or low folate levels, for elderly patients with dementia and folate deficiency, and for patients with depression and alcoholism. Partial- and non-responsive patients using an SSRI benefited from adjunctive 5-MTHF (Fava and Mischoulon 2009). The recommended dose of specific MTHF (Deplin – PamLab) is 7.5 mg once per day. Our recent study found that a dose of 15 mg/day separated from PBO, while the 7.5 mg/day dose did not. A starting dose of 7.5 mg/day may be acceptable, but 15 mg/day may be an optimal dose. Further controlled studied are needed.

Lithium

Moving from the cutting edge of clinical science – MTHF as one of the latest FDA approvals, we will now move to one of the most venerable, best studied, outcome-based strategies for treating resistant MDD, which is lithium adjunctive treatment.

The antidepressant mechanism of lithium is thought to result from the potentiation of the sensitization on the postsynaptic serotonergic receptors and from the presynaptic enhancement of serotonin transmission (deMontigny et al. 1983). Other hypotheses include effects on monoamine receptor sensitivity, simple additive effects of two antidepressants, lithium's effect on noradrenergic and dopaminergic systems, and promotion of neuronal health and growth factors (Heninger et al. 1983, Savitz et al. 2010, Shelton et al. 2010, Moore et al. 2009).

The literature is full of studies documenting the effect of lithium on TCA-resistant depression. The seminal report of adjunct lithium in the treatment of TCA-resistant depression comes from deMontigny et al (1981), where the response to open-label lithium was dramatic. Many results from subsequent double blind, controlled studies supported this initial finding (deMontigny et al. 1983, Heninger et al. 1983, Kantor et al. 1986).

Lithium adjunctive treatment for psychotic depression is often reported (Nelson and Magure 1986, Pai et al. 1986, Price et al. 1983). As suggested in antidepressant monotherapy with lithium, a more favorable efficacy of lithium adjunctive treatment is suggested in bipolar rather than unipolar depressives (Nelson and Magure 1986, Nelson and Papakostas 2010). The utilization of lithium augmentation in geriatric MDD patients is reported to be beneficial (Kushnir 1986, Lafferman et al. 1988). With the beginning of a new era in the treatment of depressive disorders in the early 1980s, lithium quickly became among the most clinically accepted choice of adjunctive treatment to SSRIs and, subsequently, SNRIs, despite most evidence being specific to lithium plus TCA. As a result of this clinical use, the literature became full of case reports, open-label studies, retrospective analyses and some randomized, controlled trials on the subject.

A review of 23 controlled and uncontrolled studies evaluating the efficacy of monotherapy with lithium for the treatment of depression suggests that lithium has reasonable antidepressant properties (Katona 1988). Bauer et al. (2003) reviewed 27 studies, including double blind, placebo-controlled, randomized comparator and open-label trials, and a total of 803 patients with refractory depression were augmented with either lithium or placebo. In these acute-treatment trials, the

average response rate in the lithium-augmented group was 45% versus 18% in the placebo-controlled. With particular interest in remission, Bauer et al. conducted a four-month randomized trial of lithium adjunctive treatment and found more depressive relapses (including one suicide) occurred in 47% of patients who had received placebo in addition to antidepressants (Bauer 2000), while none of the patients who received lithium suffered a relapse. Nierenberg et al (1990) conducted a systematic follow-up of 66 patients over 29 months to assess their longitudinal course. Twenty-nine percent had poor outcomes (e.g., hospitalization, suicide/death or attempt), 23% fair outcomes (return of depressive symptoms only after two weeks), and 48% had good outcomes (did not meet criteria for poor or fair), concluding that an acute positive response to lithium-adjunctive treatment predicted a good maintenance course.

More recent data from STAR*D assessed lithium versus triiodothyronine (T_3) adjunctive treatment in those who failed to achieve an adequate response to level 2 treatments (see **figure 1**) (Trivedi et al. 2006, Trivedi et al. 2006). Remission occurred in 13.2% of the lithium group and 24.7% of the T_3 group; there was no statistically significant difference between the two groups. There were higher dropout rates for side effects in the lithium group, relative to T_3. Of the subjects who achieved remission with lithium-adjunctive treatment, 55% remitted by week 4 and 66% by week 6. This data supports the efficacy of lithium-adjunctive treatment to SSRIs in a group of patients who failed to adequately remit to at least two levels of previous medication treatment (Trivedi et al. 2006, Trivedi et al. 2006).

Lithium has an extensive database for positive antidepressant effects when used in augmentation, but its negative effects on organ systems include its ability to impede the release of thyroid hormones, to impair cardiac sinus node function and the urine concentrating mechanism of the kidneys (Sadock et al. 2003). Given the potential for organ damage, informed consent and laboratory monitoring is necessary.

Thyroid hormone

For over a century, it has been reported that depression is associated with thyroid abnormalities. Both hypo- and hyperthyroid states are correlated with affective disturbances. The first studies examining the effects of thyroid hormones in treating MDD were conducted in the 1950s, and showed an improvement in symptoms following the use of triiodothyronine (T_3) (Flach et al. 1958, Feldmesser 1958). Prange et al (1969) reported on the effects of thyroid hormones in depression using controlled, double-blind designs. Results suggest shortening the latency of TCA onset of action and greater antidepressant activity in TCA-resistant patients. The addition of thyroid hormone to TCA in euthyroid patients also increased the efficacy of TCAs (Wilson et al. 1970, Wheatley 1972, Coppen et al. 1972). The usual dose of T_3 was 25 µg/day, and imipramine and amitriptyline were the TCAs most often used (Banki 1975, Banki 1977, Earle 1970, Ogura et al. 1974, Tsutsui et al. 1979, Goodwin et al. 1982, Thase et al. 1989, Sokolov et al. 1997, Aronson et al. 1996, Joffe et al. 1993 and 1990). One study suggested T3 hormone might be more effective than T4; 53% of subjects responded to T_3, whereas 19% responded to T_4 (Joffe et al. 1990).

There are three cases reported in the literature of MAOI/T_3 combination efficacy in MAOI-resistant depression. The first report involves a rapid alleviation of depressive symptoms when T_3 was added to a combination of phenelzine and thiothixene (Hullet and Bidder 1983, Jaffe 1988).

Nearly all of the reports of using T_3 in doses between 25-50 µg/day added to TCAs have found this combination to be safe. There are no reports of increased serious side effects caused by the individual agents nor any unusual side effects (Prange et al. 1969, Tsutsui et al. 1979, Goodwin et al. 1982). T_3 does not have any apparent effect on the TCA blood serum levels (Glassman and Perel1, 1973). T_3 has the potential to be associated with cardiotoxic effects, and the use of catecholamine-enhancing antidepressants has increased cardiovascular effects (atrial arrhythmias) in hyperthyroid states. With that stated, the combination of TCA and T_3 in therapeutic doses does not appear to have widespread cardiac effects, but informed consent and monitoring of levels and EKGs are warranted (Tsutsui et al. 1979, Goodwin et al. 1982). Additionally, long-term use may be associated with an increased risk of osteoporosis (Zajecka and Fawcett et al. 1991).

The mechanism of T_3 in potentiating anti-depressant response is speculative, but suggests synergism between T_3 and catecholamines perhaps by metabolically boosting available neurotransmitter akin to MTHF described earlier. Another suggested mechanism proposes that thyroid hormone increases the sensitivity of the noradrenergic beta-receptors and, thus, improves the existing pool of catecholamines thought to be underactive in the onset of depression (Whybrow and Prange 1981, Loosen and Prange 1982). Certain patients may inherit a genetic vulnerability to thyroid problems and depression (Panicker 2009) where this augmentation strategy may be of more benefit.

Buspirone

Buspirone is a novel anxiolytic with agonist properties at the 5HT-1A receptor and possible activity at the $5HT_2$ receptor, as well as the D2 receptor (Schatzberg and Nemeroff, In Press). Although it is used primarily in the treatment of generalized anxiety, buspirone has been considered a safe augmentation alternative in the treatment of depressive disorders (Schatzberg and Nemeroff in press, Sramek et al. 1996). The efficacy of buspirone as a monotherapy for depression with comorbid generalized anxiety disorder (GAD) in doses up to 90 mg/day has been demonstrated (Rickless et al. 1990, Robinson et al. 1990). Buspirone has also been used to reduce SSRI-induced sexual dysfunction based on the hypothetical role of modulating an imbalance of serotonin, dopamine and norepinephrine (Norden 1994).

Landen et al.'s placebo-controlled trial of buspirone in combination with an SSRI in the treatment of patients with treatment-refractory depression (1998) revealed no difference between treatment groups;

neither were there differences in the frequency of adverse effects. In a less refractory population, Appelberg et al. completed a placebo-controlled study of SSRI non-responders (2001), and found no significant response difference between buspirone and placebo. Of note, patients with initially high Montgomery-Asberg Depression Rating Scale (MADRS) scores (greater than 30) showed a greater reduction (ρ=0.26) in the buspirone group compared to those in the placebo group, suggesting that patients with greater illness may respond preferentially. No significant side effects were noted in either the placebo or the buspirone group (Appelberg et al. 2001). The data from STAR*D has provided data on the second level of treatment (**figure 1**) relative to the use of buspirone-adjunctive treatment compared to bupropion SR combination treatment, or CBT adjunctive to citalopram after failing to adequately respond/remit to monotherapy. This was the first level of switch/adjunctive treatment/combination offered to any patient who either showed inadequate response/remission, or who was unable to tolerate a 14-week trial of citalopram during level 1 (Trivedi et al. 2006, Rush et al. 2006, Trivedi et al. 2006). All three treatment groups showed similar (not a statistically significant difference) remission rates based upon QIDS-SR criteria but, unlike the previous trials, there were higher dropout rates for the buspirone-adjunctive treatment group (20.6%) compared to the others. Additionally, overall in STAR*D, the adjunctive treatment/combination group did better than did patients who had the citalopram switched to another monotherapy antidepressant at this level (Trivedi et al. 2006, Rush et al. 2006).

Clinically, our group also believes that there may also be a group of patients who may tend to become more "resistant to treatment" when switching (stopping one medication and starting a new treatment), rather than augmenting/combining treatment to an incomplete response/remission. While it is necessary to study buspirone further for potential antidepressant effect (given its open-label study successes and controlled study failures), it may be of great value for its safety and low incidence of adverse effects. In addition, this medication may be considered for use in patients who have residual or comorbid anxiety symptoms or iatrogenic sexual dysfunction associated with the use of the primary antidepressant.

Lamotrigine

Lamotrigine is currently FDA-approved for use in the prevention of relapse/recurrence of both mania and depression in bipolar disorder patients (Calabrese et al. 2003). Additionally, lamotrigine may be efficacious either as a monotherapy or as an adjunctive treatment for depression – either bipolar or unipolar subtypes – and has shown efficacy in lengthening time to depressive relapse in individuals diagnosed with bipolar disorder at a dose of 200 mg/day (Stahl et al. 2008). Its favorable adverse-effect profile (lack of weight gain or sexual dysfunction) has catapulted this treatment into the realm of antidepressant adjunctive treatment and, in some cases, has been used successfully as a monotherapy in the treatment of depressive disorders. That said, lamotrigine has little published randomized placebo controlled data in the area of treatment of unipolar depression, and reviews have suggested that it has more failed than successful monotherapy trials.

Theoretically, lamotrigine's mechanism of action may be to modulate glutamate and other transmitters, may increase plasma serotonin levels, and appears to be a weak inhibitor of $5HT_3$ receptors (Stahl 2008). Barbee and Jamhour conducted a retrospective chart review of lamotrigine-adjunctive treatment in chronic or recurrent unipolar MDD patients who had failed to respond adequately to at least two previous trials of antidepressants (2002). Response rates were: 40.5% "much or very much improved", 21.6% "mildly improved", and 37.8% "unchanged" (Barbee and Jamhour 2002). Normann and colleagues evaluated lamotrigine as an adjunct to paroxetine for acute depression in a placebo-controlled, double blind study conducted in 2002. Adjunctive treatment with lamotrigine did not result in a significant difference in HDRS total score at endpoint; it did demonstrate significant reductions in core depressive symptoms (depressed mood, guilt feelings, work and interest). In addition, patients receiving lamotrigine had fewer days on treatment with benzodiazepines and fewer withdrawals for treatment failure. The results of these two studies (Barbee and Jamhour 2002, Normann et al. 2002) and a recent review (Thomas et al. 2010) suggest that lamotrigine may be efficacious as an adjunctive treatment, especially in patients with shorter duration depression and fewer antidepressant trials (Barbee and Jamhour 2002). Lamotrigine may accelerate onset of action when given in combination with antidepressants (Normann et al. 2002).

These augmentation results must be evaluated cautiously in light of additional studies of lamotrigine monotherapy. Calabrese et al. published an analysis of five double-blind placebo-controlled monotherapy trials in bipolar depression (2008). Adults with bipolar I or II depression were treated and lamotrigine did not differ from placebo on primary efficacy endpoints (HDRS-17 item, MADRS) in four out of five studies. This agent, like buspirone, appears to have weak but positive effect sizes, and further, offers low risk of day-to-day side effects when considering risk-benefit analyses. Development of serious rash is the leading informed consent and monitoring issue for this agent.

Stimulants

It has long been known that stimulants such as amphetamine, methylphenidate and pemoline have mood-elevating effects. Amphetamine is an indirect-acting sympathomimetic agent with some direct agonist properties, which exerts its stimulant properties via direct neuronal release of dopamine and norepinephrine, blockade of catecholamine reuptake, reversal of the reuptake dopamine pump, and weak monoamine oxidase inhibition (Biel and Boop 1973). Methylphenidate is structurally and mechanistically related to amphetamine, but has less ability to release dopamine synaptically (Chiarello and Cole 1987), and pemoline is a stimulant hypothesized to augment catecholamine

transmission (Chiarello and Cole 1987). A review of the use of stimulants in the treatment of MDD demonstrates several uncontrolled reports and little controlled data supporting the antidepressant effects of this treatment, either as monotherapy or as an adjunctive treatment strategy.

Extant data appear to support stimulants more as adjunctive treatment rather than as monotherapy for depression (Zajecka and Fawcett 1991, Satel and Nelson 1989). One reason for the lack of data and trials is the risk of addiction with these agents often discourages large trial development. In small, open-label trials, adjunctive treatment of TCAs with methylphenidate or dextroamphetamine is suggested to be effective in rectifying TCA monotherapy failures (Wharton et al. 1971, Wagner and Klein 1988). An uncontrolled study in 2009 also found that methylphenidate or dexamphetamine administered adjunctively or as monotherapy to treatment-resistant depressed subjects produced "some" to "distinct" improvement in depressive symptoms among 64% of subjects (Parker and Brotchie 2009). The aggressive and somewhat risky combination of MAOI's with stimulants in treatment-resistant depression is frequently avoided following reported cases of hyperthermic and hypertensive crises (some fatal) cited in the literature (Krisko et al. 1968, Mason 1962, Dally 1962, Zeck 1961).

However, there is more recent evidence that the combination of MAOI's and stimulants may prove to be both safe and effective in treatment-resistant patients when used properly. Feighner et al. (1985) treated 13 patients with intractable depression who responded to the addition of amphetamine or methylphenidate to an MAOI with or without a TCA. Side effects included orthostatic hypotension and, in three patients, anxiety, restlessness, agitation or irritability (Feighner et al. 1985). Two patients complained of dizziness, nausea, impairment of short-term memory and insomnia, while one patient developed hypomania (Feighner et al. 1985). Our group reported a retrospective study of depressed patients who were augmented with either pemoline (no longer available) or dextroamphetamine after a partial or complete nonresponse to an adequate trial of an MAOI for a mean time of 22.3 months (Fawcett 1991). Based on Clinical Global Impression (CGI) scores, 78% had a good response to at least one stimulant plus MAOI, with 53.8% reporting being "very much" or "much improved" (Fawcett 1991). It should be noted that 3 out of 32 patients developed manic episodes (Fawcett 1991). There was no evidence of serious adverse events. We would like to emphasize that these specific cited references should be reviewed carefully because there is risk of hypertensive crisis if inaccurate application is used.

In an attempt to avoid the two- to four-week onset latency typically associated with TCAs, Gwirtsman et al. conducted a three- to four-week open-label trial of 20 depressed patients in which both TCA therapy and methylphenidate were started concurrently (1994). By the end of week 1, 30% of the patients responded to the TCA + methylphenidate hydrochloride and 63% responded by the end of week 2. These studies were uncontrolled and used concomitant psychotropics, including TCAs, thyroid enhancement, lithium and other mood stabilizers. It is possible that the safety of adding a stimulant to an MAOI may be enhanced with concomitant use of a TCA, because there is evidence that the use of amitriptyline may protect against potential tyramine reactions (Pare et al. 1982), however, not all of the patients were on TCAs in these trials. There is a positive report of one case using amphetamine to potentiate the antidepressant effects of fluoxetine (Linet 1989). We reported on eight patients who had been given methylphenidate in addition to fluoxetine with a sustained antidepressant response for at least six months in two of the patients (Zajecka et al. 1991). We additionally reported on a case where pemoline was added to fluoxetine with a sustained antidepressant response in one patient who had failed a number of other adequate antidepressant trials, some of which included pemoline augmentation. None of these cases had adverse events.

The use of stimulants for medically ill, depressed patients in uncontrolled reports indicates a potential therapeutic role for this population of patients given the clinically rapid responses reported (Biel and Boop 1978). Finally, evidence indicates that the use of stimulants may combat the hypotensive effects of conventional antidepressants (Wharton et al. 1971). On the whole, the use of stimulants in the treatment of depression demonstrates little evidence of tolerance issues (Biel and Boop 1978). Our own experience with the use of stimulants also suggests little evidence for abuse potential when used judiciously. The use of stimulants plays a very important potential role in the treatment of depressive disorders, particularly in patients with treatment-resistant depression or depression associated with low energy, avolition, anhedonia or comorbid attention-deficit hyperactivity disorder (ADHD). Obviously, well-controlled studies are needed to elaborate on their potential safety and efficacy.

Atypical antipsychotics

The depression augmentation strategies reviewed above have clinical acceptance but very few controlled positive studies to fully support their widespread polypharmacy practice. Exceptions include cases where other strategies have failed or better tolerability is needed. In the case of atypical antipsychotic medications, however, the last few years have added a more bona fide evidence base by way of the growing literature of controlled trials and FDA approvals on the use of the atypical antipsychotics as adjunctive treatment to an antidepressant medication. Atypical antipsychotics act primarily by blocking the D_2 and $5HT_{2A}$ receptors providing antipsychotic, anti-manic, and anti-neuromuscular side effects. $5HT_{2A}$ and $_{2C}$ receptor antagonism may promote dopamine and norepinephrine activity in the frontal cortex as well. They may also modulate, in varying degrees, several additional serotonin sub-receptors (such as $5HT_3$, $5HT_{1b}$, $5HT2_b$) and inhibit the reuptake of norepinephrine and serotonin similar to SSRI and SNRI antidepressants. Uniquely, aripiprazole partially agonizes the DA_2 and DA_3 receptors, effectively promoting increased dopaminergic tone. These have theoretical antidepressant effects. Some agents block

H_1 histamine receptors, and this action is utilized by FDA-approved hypnotic agents and anxiolytics. Further, in subjects with treatment-resistant depression, statistically significant increases in brain-derived neurotropic factor (BNDF) plasma levels of have been observed upon adjunctive use of atypical antipsychotics with various classes and antidepressant medications (Yoshimura et al. 2010).

Each drug in the atypical class possesses a unique receptor profile, which can help the physician target the appropriate therapy for each individual patient. Some of the above mechanisms acting at serotonin sub-receptors also apply to certain FDA-approved antidepressants (e.g., mirtazapine, nefazodone, trazodone), increasing the possibility that the atypical antipsychotics may be effective treatments for anxiety and depression. The atypicals' evidence base will be discussed next, but they also possess many pharmacodynamic properties that a modern day psychopharmacologist must be aware of to pick the best drug for each patient. Some have more antidepressant effect, more antipsychotic effect, more sedation, or more activation – all based upon receptor affinity profiles. Many of these agents have antipsychotic or anti-manic effects at high doses and antidepressant effects at lower doses. The future or advanced current psychopharmacologist should be aware of these minor properties, which may lend nuance to treating each individual patient (Schwartz and Stahl in press).

In regards to the atypicals in depression, Barbee et al. conducted a retrospective chart review to determine the effectiveness of olanzapine, risperidone, quetiapine and ziprasidone as adjunctive treatment agents in patients with treatment-resistant depression (2004). The overall response rate was 65%. With regard to side effects, it was found that weight gain was associated with olanzapine; nausea, anxiety, depression were associated with risperidone; and sedation was associated with quetiapine and ziprasidone. Nelson and Papakostas (2010) conducted an extensive meta-analysis of RCTs investigating atypical antipsychotic augmentation in major depressive disorder resistant to previous treatment. Results indicated that atypical antipsychotics are significantly effective augmentating agents in treating MDD, but do involve a notable side-effect burden. The authors also noted that efficacy did not significantly vary between the atypical antipsychotic medications tested (namely, olanzapine, risperidone, quetiapine, aripiprazole) (Nelson and Papakostos 2010). Increasing data suggest that the use of some atypical antipsychotics appears to cause a higher incidence of metabolic disorders. With increased data and approvals, more of these agents are being used. Outside of monitoring for extrapyramidal and tardive dyskinesia, it is recommended to monitor metabolic parameters at baseline and at regular intervals with all atypical antipsychotics (American Psychiatric Association and American Diabetes Association guidelines 2004). With regard to the above-stated suggestion, the clinician must use careful judgment in the administration of these drugs in combination with antidepressant medications, coupled with patient education and regular monitoring. Moreover, because these are dopamine-blocking drugs, the typical warnings exist for the monitoring of all extrapyramidal syndromes.

With regard to individual agents, Tohen et al. initially reported that olanzapine as monotherapy, or in combination with fluoxetine, produced a greater reduction of core depressive symptoms compared to placebo in Bipolar I depressed patients (2003). Shelton et al. conducted a double-blind trial of olanzapine with fluoxetine versus either agent alone with treatment-resistant unipolar depression (2001). Olanzapine plus fluoxetine produced significantly greater improvement than either monotherapy from baseline. Increased appetite and weight gain occurred among patients treated with olanzapine. There were no differences between treatment groups with regard to extrapyramidal symptoms (EPS) or adverse drug interactions. Thase et al. replicated these findings in a group of unipolar depressed patients (2006), yet subsequent trials failed to replicate the findings (Corya et al. 2006, Shelton et al. 2005). Overall, the evidence in support of the olanzapine-fluoxetine combination earned FDA approvals for bipolar depression and for treatment resistant MDD. Olanzapine is a relatively simple atypical and does not possess SSRI, NRI, 5HT1a agonism, and is not an accepted monotherapy for depression, but with the added SSRI potential of fluoxetine, it has well-controlled trials and regulatory data supporting its use in depression.

Hirose and Ashby completed an open-pilot study of fluvoxamine plus risperidone as an initial antidepressant therapy (2002) where 76% achieved remission, 17% achieved response, and two were not responsive. Adverse effects were mild, without cases of EPS, nausea or vomiting. Two subsequent open-label studies also showed risperidone's efficacy in patients who failed to respond to monotherapy SSRI (Gharbawi et al. 2006, Keither et al. 2006). Keither et al. reported on a controlled study in which MDD patients who were not responsive to antidepressant monotherapy were randomized to risperidone or placebo. Subjects in both groups improved significantly, however, the odds of remitting were significantly better for patients in the risperidone arm than for those in the placebo arm (Keither et al. 2006). In an open label trial conducted by Papakostas et al. patients with MDD who had failed to respond to an adequate trial of an SSRI were treated with ziprasidone (2004) and at the end of the trial, 61.5% were classified as responders and 38.5% with remittance. The use of ziprasidone appeared safe with no severe adverse events and no clinically significant QTc prolongation. Dunner et al. reported on a group of MDD subjects who were randomized to single-blind continuation of monotherapy sertraline or received ziprasidone adjunctive treatment (2007). There was a significant improvement in the adjunctive treatment group compared to the monotherapy sertraline. Of note, the remission rate in the sertraline/ziprasidone 160 mg/day group was 21% and 5% for the other two groups.

Aripiprazole

Aripiprazole was the first pharmacological agent to receive formal FDA prescription approval (2007) as an adjunctive treatment for inadequate response to a monotherapy antidepressant. The standards for this prescription approval are considered higher than the

medical food standards applied to methylfolate discussed earlier. In addition to the 5-HT modulating effects via the $5HT_{2A}$ blockade and $5HT_{1A}$ stimulation of these receptors, aripiprazole has a unique pharmacological property as a "partial" dopamine receptor agonist as well (as noted above). Our group reported on the augmenting effects of aripiprazole to poor responders to SSRI or venlafaxine XR monotherapy for unipolar depression (Zajecka et al. 2005) with resultant mean HDRS score reduction at endpoint of 10.8. Open-label prospective trials replicated this result (Schwartz et al. 2007).

Successful pilot studies then led to fully controlled regulatory trials. These trials have shown definitive efficacy of aripiprazole as an adjunctive treatment agent and with less stringency as a monotherapy in patients with treatment-resistant depression (Simon and Nemeroff 2005, Worthington et al. 2005, Schwartz et al. 2007, Papakostos et al. 2005, Patkar et al. 2006, Adson et al. 2005, Pae et al. 2006). These studies have shown the onset of aripiprazole activity as early as week one of treatment, at doses lower than those used in schizophrenia or mania. A study conducted by Berman et al (2007) found remission and response rates to be higher in the aripiprazole augmentation group versus placebo (15.7% versus 26.0%) and (23.8% versus 33.7%), respectively. The mean dose of aripiprazole in this trial was approximately 11 mg/day with akathisia being a leading side effect.

Our group has found success in starting patients on low doses (occasionally only 1 mg/day) and gradually increasing the dose to minimize akathisia. Other aripiprazole controlled trials have replicated its augmentation efficacy, and still other studies suggest efficacy in bipolar disorder (McIntyre 2010, Thase et al. 2008) as monotherapy or adjunctively to antidepressant medication. Reviews and meta-analyses (Nelson et al. 2010, Papakostas 2009, Arbaizar et al. 2009) of the data have also supported the efficacy of aripiprazole in this population.

Quetiapine

Quetiapine is now likely the next-most-extensively studied atypical antipsychotic in the treatment of bipolar and unipolar depression, and a leader in the evidence-base, along with lithium controlled data. Early trials assessed quetiapine immediate release, while more recent trials have used the extended release version (XR). A unique combination of direct and indirect pharmacological actions mediated with quetiapine and its active metabolite, norquetiapine, may underpin its clinical antidepressant properties. The high affinity and inhibitory actions on the norepinephrine transporter and potent $5HT2_{A,C}$ receptor antagonism, $5HT1_{a}$ receptor agonism and histamine-1 receptor antagonism give it the theoretical potential to ameliorate psychosis and mania, and also depression, anxiety, and insomnia (Goldstein et al. 2007).

Early open-label trials supported the efficacy of a range of doses (50 mg and above) of quetiapine to improve antidepressant efficacy in partial responders. At lower doses (less than 150 mg/day), the augmenting antidepressant effects of quetiapine for partial responders to monotherapy antidepressants may have been partly due to rapid improvement of sleep, anxiety or improving sexual function. However, higher doses (i.e., ≥ 150 mg/day) may provide a broader pharmacological profile on the serotonin, dopamine and noradrenergic systems that may, in turn, provide a more direct antidepressant effect. This effect has been demonstrated in both bipolar depression monotherapy and in MDD augmentation studies (Goldstein et al. 2007).

Quetiapine was the first pharmacological treatment to receive FDA-approval as a monotherapy for the depressed phase in bipolar I and II. Two consecutive controlled trials supported this efficacy (Calabrese et al. 2005, Thase et al. 2006) and two additional large, placebo-controlled trials also support the use of quetiapine XR as an adjunctive treatment for inadequate response to various antidepressants in MDD (El-Khalili et al. 2008, Early et al. 2007). Side effects observed included higher rates of sedation, somnolence, dizziness, weight gain and metabolic issues increasing when doses exceed 150 mg/d. Our group may start quetiapine at the lower dose range, but then increase doses toward 300 mg/day as either a monotherapy or adjunctive treatment. Use of quetiapine XR allows for once-per-day dosing in the evenings.

Psychopharmacologists must be aware of the evidence-base and the drug's mechanism of action in order to choose medications appropriately, but also must be aware of even the technology that goes into making pills. Instant-release drugs have a higher initial side-effect burden (i.e. sedation within 30 minutes of administration) whereas slow-release products allow for lower plasma levels, and less severe side effects that may linger into the day. Immediate-release quetiapine is given at bedtime, and the high drug-plasma levels allow greater initial sedation, which may promote sleep (a "side-effect" if sleepiness occurs during the day, but a positive clinical effect if insomnia is successfully alleviated at night). The slow-release product is given 4 hours before bedtime as peak plasma levels and sedation occurs later. Some patients require the hypnotic effect and prefer the immediate release and others who prefer to avoid daytime sedation may choose the slow release.

Benzodiazepines

Over 60% of patients with depression suffer from anxiety and/or insomnia symptoms. Residual anxiety symptoms are common, and can potentially significanlty aggravate the depression; anxiety remains one of the greatest predictors of imminent suicide in depression. Benzodiazepines are effective anxiolytic medications offering rapid reduction in anxiety symptoms. These drugs are positive allosteric modulators, where they facilitate the activity of GABA-A receptors, which allows more neuronal chloride influx and neuronal dampening. This dampening allows for anxiolysis or hypnosis depending which neuroanatomic area is inhibited (Stahl et al. 2008).

Perhaps unfortunately, many negative perceptions about this class exist secondary to concerns regarding abuse potential. This can be a barrier to electing to

utilize these highly effective medications. The role of acute reduction of anxious symptoms in the treatment of depression is important. However, there is little data on long-term clinical use for anxiety secondary to depression or in the treatment of residual and/or comorbid anxiety.

Benzodiazepine adjunctive treatment may be one of the more popular strategies employed by physicians, although there is little data to support it, and little data to refute this strategy. If one were to consider the HDRS, about one third of the items on this scale would count as "anxiety symptoms" and sedatives are felt to be effective in quickly lowering symptoms in this domain. Furukawa et al. completed a meta-analysis of nine controlled studies to determine whether antidepressant plus benzodiazepine treatment was more efficacious than treatment with antidepressant alone MDD (2001). Based on intent-to-treat analysis, the combination group was more likely (63% versus 38%) to show a response. Smith et al. completed a controlled study where markedly or moderately ill MDD subjects were given fluoxetine plus placebo or fluoxetine plus clonazepam (1998). The improvement in MDD scores was more significant in the adjunctive clonazepam treatment group. No serious adverse events were found in either treatment group. Taper effects were modest and transitory.

Pindolol

Pindolol is a beta-adrenergic blocker that is also both an antagonist and partial agonist at 5HT1A receptors (Stahl et al. 2000). It has been theorized that pindolol can immediately disinhibit serotonin neurons, increasing their output, which has lead to the proposal that it may be a rapid onset antidepressant, or a facilitating or augmenting agent (Stahl et al. 2000). There are clinical studies that do suggest that pindolol adjunctive treatment may speed the onset of action of SSRIs, but there is little additionally supportive data. Isaac conducted a controlled trial in which subjects were given milnacipran plus pindolol or milnacipran plus placebo (2003). Improvement was greater in the pindolol group. Perez et al. conducted a single-blind trial comparing fluoxetine plus pindolol and fluoxetine plus placebo (2001). At endpoint, the response rate in the fluoxetine plus pindolol group and the percentage of remitted patients were 15.6% and 15.4%, respectively, both greater than the placebo arm. There was no difference between groups in side effects in this study. Perez et al. conducted another controlled trial of pindolol adjunctive treatment in MDD patients resistant to SSRI monotherapy (1999). At the end point, there were no significant differences. Berman et al. completed a controlled trial in which patients were concurrently treated with fluoxetine and either placebo or pindolol for six weeks (1997) also with no differences.

Recent data supports the use of pindolol as an augmenting agents for SSRIs, perhaps especially for use with index-episode cases. Duration of untreated episode (DUE) is thought to predict quality of response to treatment. Diego-Adeliño et al. studied treatment naïve and recurrently depressed patients and found, primarily, that shorter DUE predicts greater sustained response to antidepressant treatment (2010). The authors found, secondarily, that pindolol speeds the beneficial effect of SSRI antidepressants (i.e., fluoxetine and citalopram). Portella et al (2009) found similar results in their related study. Geretsegger et al. found that, while unipolar patients treated with paroxetine and pindolol did not separate from placebo, both treatment naïve and bipolar patients did "significantly benefit from pindolol augmentation" (2008).

Modafinil

Modafinil is a novel stimulant medication that is FDA-approved for the treatment of narcolepsy, obstructive sleep apnea syndrome and shift-work sleep disorder, and is often used for fatigue associated with multiple sclerosis, cancer, and MDD. A putative minor mechanism of action is thought to be mildy increasing the level of dopamine by inhibiting its reuptake, because this drug requires an intact dopamine system to function. Modafinil has some additional pharmacodynamic similarities to typical stimulants, but also is unique (Stahl et al. 2000) as it may also enhance histamine release from the tuberomammilary nucleus into the frontal cortex in a system that parallels the reticular activating system where true stimulants work. This circuitry may enhance activity of the dorsolateral prefrontal cortex, which is required for proper executive functioning and cognitive processing. Deficient function in this system may account for poor concentration, indecision, ambivalence, or fatigue.

The net effect of modafinil may be enhancement of cognitive arousal, alertness, and concentration (Stahl et al. 2000). Modafinil has, therefore, been called a "histamine alerter." In addition, modafinil may decrease GABA transmission, which lowers CNS inhibition and results in activation (Ferraro et al. 1996). Modafinil is well tolerated, with minimal abuse potential but is classified as a C-IV controlled drug in the U.S. Our group has found modafinil to be quite helpful in the treatment of fatigue associated with depression or fatigue associated with the use of other psychotropic medications or other comorbid illness (Schwartz 2004a and b, Schwartz et al. 2002). DeBattista et al. completed a controlled study (2003) wherein patients received once-daily modafinil or matching placebo as an adjunct to antidepressant therapy. Modafinil rapidly improved fatigue and daytime wakefulness, however, there were no differences after the sixth week so the drug appeared to be an accelerant. Modafinil was well tolerated when administered in combination with a variety of antidepressants. This data suggests that modafinil is an early response-facilitating agent, which has been replicated by Ninan et al (2004).

Less stringent studies include Menza et al.'s retrospective case series (2000) of seven patients with depression treated with modafinil to augment a partial or nonresponse to antidepressants; all seven patients achieved full or partial remission within one to two weeks. DeBattista et al. completed a four-week open-label study where improvements were significant initially, but not by the end of four weeks (2004). The study suggested that modafinil is effective in facilitating or accelerating antidepressant response and could also

address fatigue, effort, and overall depression level. The Eppworth Sleepiness Scale and Fatigue Severity Scale showed improvement when sleep and fatigue were studied. Shelton and colleagues' review of therapeutic options for treatment-resistant depression supported "beneficial effects of modafinil for patients affected by TRD, especially those patients who report fatigue and sleepiness". The authors cite nausea, headache and dizziness as most common side effects of this generally well-tolerated medication (2010). Further studies are needed to ascertain effects on other core depressive symptoms, as well as long-term efficacy, safety and tolerability.

Steroid hormones

Dysfunction of the hypothalmatic-pituitary-adrenal (HPA) axis has been implicated in the pathophysiology of depression. Depression associated with thyroid abnormalities and the depressogenic effects of progesterone (i.e., oral contraceptives) (Malek et al. 1976) and other steroids support a link between the endocrine system and affective disorders. The use of estrogens in females for the treatment of post-menopausal depression has also been reported to be effective (Frank et al. 1936, Vogel et al. 1978). This use of estrogens for the treatment of depressed women is of interest in that there is evidence for increased monoamine oxidase activity in premenopausal depressed women, and estrogen normalizes this activity and improves depressed mood (Klaiber et al. 1972, Wiesbader and Koszrok 1938). These results suggest that a decrease in estrogen level may increase the catabolism of monoamines (a lowering of serotonin, norepinephrine or dopamine, which may ultimately cause receptor upregulation and resultant MDD). It is further suggested that the combination of anti-depressants to increase available monoamine, when combined with estrogen (which decreases monoamine oxidase activity) may be an effective treatment for depressed female patients of premenopausal or menopausal age (Ananth and Ruskin 1974).

There are mixed reports in the literature on the use of estrogen for depressed women in varying phases of their reproductive life cycle. The idea of using estrogen for depression was first introduced based on the observations that estrogen levels decrease during menopause and fluctuations are seen at other periods of the reproductive cycle. Some models suggest that estrogen may modulate serotonin, catecholamines, and even cortisol activity, all implicated to play a role in depression (Schatzberg and Nemeroff in press, Klaiber et al. 1972, Wiesbader and Koszrok 1938, Fischette et al. 1984, Klaiber et al. 1979, Stahl 1996). While it is possible, from examination of current data, that the onset of major depression is increased after menopause, there is little evidence that estrogen alone is effective in the treatment of depression in postmenopausal women (Hirchfeld et al. 1997). Four significant studies have found no improvement of depression in response to treatment with estrogen as a monotherapy (Schneider et al. 1977, Shapira et al. 1985, Coope 1981, Coope 1975, Prange 1972). However, there is evidence that estrogen might be effective as an adjunctive treatment for depressed postmenopausal women and in postmenopausal women resistant to TCAs or SSRIs (Stahl 1996, Schneider et al. 1977). Schneider et al. pooled 127 women over 60 years old who were treated with sertraline with and without estrogen-replacement therapy and reported on two controlled trials in MDD (2001). Sertraline-treated women taking estrogen had significantly greater global improvement (79% v. 58%) and better quality of life than those not receiving estrogen. There was no reported difference in side effects between the estrogen and non-estrogen groups.

Clinicians are advised to consider the potential risks and benefits of using estrogen replacement in peri- and post-menopausal females (e.g., personal/family history of breast cancer), especially in women who have residual symptoms or exacerbation of symptoms.

Testosterone

There is little data on testosterone as an augmenting agent in the treatment of depression. Testosterone is used to enhance libido in both men and women. In hypogonadal men, testosterone may improve mood and energy. In general, testosterone alone as an antidepressant has shown inconclusive results. Nineteen subjects completed a controlled study in which Pope et al. administered either transdermal testosterone gel or placebo to men with refractory MDD and low or normal testosterone levels (2003). Each subject continued his existing antidepressant regimen. Efficacy analysis revealed that the testosterone-treated patients had a significantly greater rate of decrease in scores on both the HDRS and CGI than did the placebo-treated patients. One additional report demonstrated onset of paranoia and aggression when methyltestosterone was added to augment imipramine (Wilson et al. 1974). Miller et al. conducted an open-label pilot study of low-dose transdermal testosterone to nine women with treatment-resistant depression, where response was achieved by two-thirds and remission by one-third of subjects (Miller et al. 2009). Further studies are needed to ascertain the potential role of the use of testosterone as an adjunctive treatment for depression in males with normal and low testosterone levels. In patients with low baseline levels of testosterone, it is important to assess for potential comorbid illness and iatrogenic causes prior to initiating treatment. Ascertaining baseline and follow-up serum testosterone levels is suggested; consideration of potential risks including irritability, aggression, prostate enlargement and hepatic effects.

Cortisol Blockers

A significant, developing, antidepressant strategy directly targets the HPA axis. Abnormalities of the HPA axis were among the first and most consistently identified findings in depressed subjects. Such findings include elevated CSF corticotrophin-releasing hormone (CRH) levels, elevated cortisol levels, and diminished sensitivity to dexamethasone suppression. In preclinical and clinical studies, chronic antidepressant treatment normalized these findings. Therefore, agents that

directly reduce hypercortisolemia in depressed subjects were tested for antidepressant activity (Schatzberg and Nemeroff in press, Murphy and Wolkowitz 1993). Two open trial studies (Murphy and Wolkowitz 1993) have evaluated steroid suppressant therapy (including metyrapone, ketoconazole and aminoglutethimide) in treatment-refractory patients. Results are promising but preliminary, with the need for more data. There is one randomized, controlled study in the literature evaluating the effect of metyrapone or placebo plus SSRI. Results showed a higher proportion of patients receiving metyrapone had a positive treatment compared with placebo patients. While this study supports the use of metyrapone as an accelerant to the onset of antidepressant action when added to an SSRI, further study on long-term efficacy is warranted (Jahn et al. 2004).

SAMe

S-adenosyl-l-methionine (SAMe) is an endogenous substance in mammalian tissue that shows potential mood-elevating effects in man (Baldessarini 1987). SAMe is approved as a depression treatment in Europe; it does not have any such indication in the U.S., but is widely available over-the-counter. SAMe has medicinal usefulness in several disorders, particularly osteoarthritis (Marcolongo et al. 1985). The first mood-elevating effects of SAMe were discovered serendipitously in the 1970s, when the substance was being investigated for use in the treatment of schizophrenia, and was found to have mood-elevating properties (Rosenbaum et al. 1988, Lipinski et al. 1984).

Several open-label and single-blind trials suggest antidepressant effects of SAMe when using intravenous or intramuscular routes of administration (Lipinski et al. 1984, Agnoli et al. 1976). Several double-blind trials reported SAMe to have equal or greater antidepressant effects when compared to amitriptyline, imipramine or clomipramine (Bell et al. 1986, Miccoli et al. 1978, Scarzella and Appiotti 1977). These studies show a trend toward a more rapid onset of action and less, if any, side effects with the use of SAMe. Precipitation of mania/hypomania has been reported with the use of SAMe as well (Carney et al. 1989).

Again, its mechanism of antidepressant action remains unknown, however, the substance is an endogenous methyl donor for several CNS neurotransmitters, including serotonin, norepinephrine, and dopamine, all of which are implicated in the pathophysiology of depression (Lipinski et al. 1984). This pathway also parallels that utilized by l-methylfolate (discussed earlier) and may promote extra monoamine synthesis. SAMe also affects the lipid composition of cell membranes, which may also be involved in the pathophysiology of affective disorders (Cimino et al. 1984). SAMe increases folate activity, which, when deficient, may also be involved in the pathogenesis of depressive disorders (Reynolds et al. 1983). All of the above-mentioned studies are based on the use of intramuscular or intravenous routes of administration. The reason for the preference of this route of administration over the oral route is based on limited investigation of the pharmacokinetics of SAMe, suggesting that it has an unstable oral bioavailability. However, a recent open-label study using oral SAMe suggests antidepressant efficacy (Rosenbaum et al. 1988). Finally, an investigation into its oral bioavailability in a stringent controlled study suggests that SAMe is a novel antidepressant agent (Papakostas et al. 2010).

Berlanga et al. completed a double blind clinical trial in 1992 to evaluate the efficacy of SAMe in accelerating the onset of action of imipramine. Forty placebo nonresponders were given either dissolved SAMe intramuscularly (IM) or dissolved placebo IM with peroral imipramine 150 mg/day. Depressive symptoms decreased earlier with SAMe-imipramine than with placebo, but this difference was only significant through the second week. Adverse effects were noted in neither the SAMe nor the placebo. While there is plenty of support for using SAMe as a monotherapy in the treatment of depression, the question of its usefulness as an adjunct has remained open until relatively recently, when Papakostas et al. published data on this regimen (2009). The authors reviewed the evidence supporting SAMe both as monotherapy and as adjunctive treatment for MDD. They found SAMe to be superior to placebo and equivalent to tricyclic antidepressants in treating patients with MDD when used intravenously or intramuscularly, and that SAMe is generally well tolerated. They found a smaller body of evidence supporting the use of oral SAMe as monotherapy for MDD. The author concluded, "[t]he most widespread clinical use for SAM-e may be as an oral augmenting agent for treating antidepressant nonresponders with MDD".

Atomoxetine

Atomoxetine was initially studied as a monotherapy for MDD in the 1980s. Unfortunately, doses were low (20 mg/day), which may have limited the potential for favorable efficacy outcomes in these early exploratory studies. Further studies with atomoxetine for MDD in the 1980s were discontinued with the advent of and enthusiasm for the SSRIs. However, interest in the role of norepinephrine in patients failing to adequately respond to an SSRI re-emerged with the approval/availability of atomoxetine for ADHD. While there may be a clinical interest in using atomoxetine as an adjunctive treatment for MDD, there is a paucity of data in the literature. One controlled study (Michelson et al. 2007) reported on the use of atomoxetine as an adjunctive treatment in TRD patients showing an inadequate response to a trial of sertraline. The outcome failed to demonstrate statistically significant differences between atomoxetine and placebo.

Because our group has found atomoxetine useful as an adjunctive treatment with partial response to SNRIs, SSRIs and other antidepressants, and we use a similar dosing strategy used in the Michelson et al. study (2007), it is worth reviewing this study's methods and outcomes. The study looked at TRD in 276 adult patients prospectively treated with sertraline (up to 200 mg/day; mean dose 161 mg/day) for 8 weeks. Patients

with no response or partial response (n=146) were randomized to atomoxetine adjunctive treatment (40-120 mg/day) or placebo for an additional 8 weeks. Completion rates were similar between the two groups, and there were no differences in discontinuation rates for side effects. There was no difference between groups in the mean change in HDRS, or in remission rates (40.3% atomoxetine/sertraline; 37.8% placebo/sertraline).

Papakostas and colleagues evaluated the efficacy and safety of atomoxetine as an adjunctive medication for residual depressive fatigue in a naturalistic treatment setting (2006). Twelve (85.7%) of fourteen patients (nine remitters, three partial responders) received at least four weeks of atomoxetine treatment. The remaining two patients discontinued atomoxetine early secondary to increased anxiety. There was a significant improvement in the Brief Fatigue Inventory and all 12 patients were remitters at follow-up. Adverse effects included insomnia, increased anxiety, nausea, and dry mouth. Reimjherr et al. (2010) published speculative findings following their trial of atomoxetine adjunctive to sertraline in patients nonresponsive to sertaline monotherapy. They propose that treatment-resistant depression "may be related to polymorphisms in the promoter region of the serotonin transporter gene (5-HTTLPR) or dysregulation of noradrenergic systems." Their study found that, of those patients having 5-HTTLPR genotype data, "significantly more S/S-genotype patients achieved remission under combined sertraline/atomoxetine treatment relative to the other genotypes (S/S=81.8%; non-S/S=32.7%), but not under sertraline/placebo treatment (S/S=35.7%; non-S/S=37.7%)".

Our group uses atomoxetine to augment partial response to SNRIs, SSRIs, mirtazapine and bupropion, and also, in patients with comorbid MDD/ADHD. We generally utilize a starting dose at approximately 40 mg/day, slowly increasing to 80-120 mg/day. If results are not seen at these doses, we will consider increasing up to 160 mg/day. Known adverse effects include anxiety, activation, somnolence, dry mouth and urinary hesitancy/retention, and reports of cycle induction have been described (Henderson 2004). Blood pressure should be monitored, especially if multiple noradrenergic agents are being combined.

Other adjunctive treatment strategies

Other adjunctive treatment strategies reported in the literature include omega fatty acids, buprenorphine, ketamine, riluzole, tramadol, dopamine agonists, anticonvulsants, vagus nerve stimulation, transcranial magnetic stimulation, electroconvulsant therapy and empirically-based psychotherapies (Papakostos 2006, Izumi et al. 2000, Bouckoms et al. 1993, Barbosa et al. 2003, Zarate et al. 2006, Sanacora et al. 2004, Zarate et al. 2005, Dietrich et al. 2000, Rogoz et al. 2004, Stryger et al. 2003, Zarate et al. 2004, Peet and Horrobin 2002, Su et al. 2003). VNS and TMS have both been recently approved by the FDA for use as adjunctive therapy (Shelton 2010).

Antidepressant combinations

Mirtazapine

Mirtazapine is a novel antidepressant with a proposed mechanism involving blockade of alpha-2 heteroreceptors facilitating norepinephrine in the CNS. There is possible dopamine release increase, combined with unique actions on several serotonin sub-receptors (5HT-2 antagonism promotes cortical dopamine/norepinephrine release, promotes deeper sleep, avoids side effects of sexual dysfunction and activation, and histamine-1 receptor blockade promotes sleep initiation and anxiolysis) (Millan et al. 2000, Stahl 2000).

Carpenter et al. completed a controlled combination study wherein mirtazapine was added to current antidepressant treatment of MDD (Carpenter et al. 2002). Forty-four percent of the subjects had clinical response to the combination approach, demonstrating statistical significance (Carpenter et al. 2002). There was no difference in side effects between groups. In another recent randomized, controlled study in MDD patients with marked somatic symptoms randomized to mirtazapine or venlafaxine, mirtazapine, findings showed similar efficacy between these in treating both depressive symptoms and somatic complaints (Kang et al. 2009). Carpenter et al. completed an open-label study where mirtazapine was added to initial monotherapy failing patients (1999). At the four-week follow-up, 55% were responders, 30% were non-responders, and 15% had discontinued, owing to weight gain and sedation (Carpenter et al. 1999). The 4th level of the STAR*D study included patients who were either intolerant or failed to show an adequate response at the previous 3 levels of treatment (**Figure 1**). Patients were randomly assigned to open-label treatment with either tranylcypromine or venlafaxine extended-release (ER) plus mirtazapine combination (McGrath et al. 2006). There were no differences between the two groups for rates of remission; however the reported side effects and attrition rate was lower with the combination group compared to tranylcypromine alone.

Because it is novel in its pharmacological action and can reduce depressive and anxious symptoms as well as adverse effects from the use of other antidepressants, our group has found mirtazapine to be of particular benefit. Mirtazapine can help decrease insomnia symptoms, sexual dysfunction and GI distress associated with SSRIs and SNRIs. The potent $5HT_3$ blockade can reduce nausea associated with acute SSRI treatment. Potential appetite increase secondary to antihistamine properties, and potential sedation can be limitations for some cases. Conversely, these effects may be beneficial for residual poor appetite or insomnia or should nausea accompany depression. Given the $5HT_3$ antagonism of this compound, however, higher doses may be associated with less sedation in some patients. Independent of its effects relative to easing depressive symptomology, mirtazapine is thought to have dampening effects on the activity of the HPA system, and specifically on the appearance of elevated cortisol levels in depressed patients and the negative sequelae associated with chronic hypercortisolemia (Scharnholz et al. 2010).

Bupropion

Bupropion is an effective antidepressant medication whose FDA approval predates the groundbreaking SSRI, fluoxetine. The antidepressant mechanism of bupropion still remains speculative, although evidence suggests that it increases norepinephrine and dopamine activity through reuptake inhibition. It is among the few available antidepressant medications without direct effects increasing 5-HT activity, so it tends to reduce weight and not promote sexual dysfunction. However, many clinicians believe that the combination of bupropion plus a serotonergic agent can be quite successful not only in terms of efficacy, but also in reducing prominent adverse effects such as sexual dysfunction, weight gain and fatigue.

Early open-label studies suggested the efficacy of bupropion when used in combination with other antidepressants. DeBattista et al. conducted an open-label trial seeking to establish the efficacy of bupropion combined with an SSRI or venlafaxine in partial and non-responders (2003). At week 6, HDRS and BDI scores were significantly reduced when compared with those at baseline (39% and 44%, respectively). Sixty-four percent of patients had ratings corresponding to "much improved" or "very much improved" by week 6 on the clinician-rated CGI. Headache and insomnia were the most commonly reported adverse effects. Lam et al. conducted an open-label cohort study comparing the effects of combining citalopram and bupropion sustained release versus switching to the other monotherapy in treatment-resistant depression (2004). The combination option showed superiority to the monotherapy, and the proportion of patients in clinical remission was (28% vs. 7%). There were no differences in the proportion of patients who had side effects. Bodkin et al. conducted a chart review of patients treated with the combination of an SSRI and bupropion (1997). Ultimately, greater symptomatic improvement was found in 70% of the subjects on the combination. Adverse effect risks were similar to those of monotherapy. Spier treated 25 consecutive patients with bupropion in combination with an SSRI or venlafaxine after either monotherapy failure or venlafaxine-induced side-effect development (1998). Fifty-six percent of the patients responded to the combination for residual depressive symptoms. Only 20% responded when the combination was given to treat monotherapy-induced side effects.

Tricyclic antidepressants/monoamine oxidase inhibitors

The combined use of TCAs and MAOIs has been suggested for years as an alternative treatment for persons with resistant depression. Theoretically, the rationale for using both antidepressant agents would be to combine the effect of the TCA-mediated neurotransmitter reuptake inhibition with the enzyme inhibition of the MAOI and, thus, bring about a maximal amount of monoamine neurotransmission at the postsynaptic receptor for all three major amines involved in the pathogenesis of depression. However, the combined use of a TCA and an MAOI is warned against in the Physician's Desk Reference (2005) on the basis of the potential for hypertensive and hyperthermic episodes associated with such combinations. It is recommended to wait for 10 days before starting a TCA after discontinuation of an MAOI or before starting an MAOI after discontinuation of a TCA. However, there are several reports of safely switching from a TCA to an MAOI within a four-day period, and of this drug combination being used safely (Kahn et al. 1989, Sethna 1974, Spiker and Pugh 1976, Schmauss et al. 1988). In fact, there is evidence to suggest that certain TCAs (particularly amitriptyline) may help protect against tyramine-induced hypertensive reactions seen with MAOIs (Fawcett 1991), however, such a drug combination should not keep the patient from adhering to a low-tyramine diet.

Early evidence of TCA/MAOI efficacy in treatment-resistant depression is derived from anecdotal reports and uncontrolled studies. Although not performed under controlled conditions, there are reports of depressed persons who failed to respond to monotherapy with TCAs or MAOIs, or who failed to sustain improvement with ECT subsequently responding to TCA/MAOI combinations (Sethna 1974, Hynes 1965, Gander 1965). Several controlled trials report that the TCA/MAOI treatment combination is not superior to either treatment alone (Razani et al. 1983, Young et al. 1979). However, even these trials do not adequately study treatment-resistant depression specifically. While the actual efficacy of the TCA/MAOI combination for treatment-resistant patients remains to be properly evaluated in controlled studies, this treatment should be utilized only when patients fail other conventional treatments. The TCAs recommended for use are the more serotonergic agents (e.g., amitriptyline, trimipramine and doxepin) (White and Simpson 1981). Although tranylcypromine is noted for increased risk of hypertensive reactions, it is reported to be safe when used in combination with TCAs, as are phenelzine and isocarboxazid (Schmauss et al. 1988, Razani et al. 1983). It is generally not recommended to use imipramine, desipramine or clomipramine, all of which possess at least some noradrenergic properties. Based on reports on the safety of TCA/MAOI combination, it can be started simultaneously, or the TCA started first and then treatment with the MAOI initiated. The use of lower doses – lower than when either drug was used alone – is recommended when initiating such a combination.

Heterocyclic antidepressants/selective serotonin reuptake inhibitors

SSRIs have claimed status as first-line treatment for depression since the 1980s; however, some patients do not fully remit, and so require further pharmacological action beyond serotonin. In the early years of the use of SSRIs, clinicians remained familiar with the use of TCAs/heterocyclics (HCAs) and commonly "overlapped" or combined treatments to achieve a "broader" pharmacological effect. Animal models and controlled/open-label reports suggested possible rapidity of response and, perhaps, a more robust response with combination relative to that achieved with

monotherapy. HCAs are metabolized via the CYP2D6 pathway and, therefore, necessitate caution when being combined with other "2D6" drugs such as SSRIs/SNRIs (fluoxetine, paroxetine, duloxetine, etc.). As with other TCAs, drug levels can be obtained five to seven days after the dosage is initiated and 8 to 12 hours after the last dose.

In an open trial completed in 1991 by Nelson et al. 14 inpatients with major depression were administered both desipramine and fluoxetine, and their responses were retrospectively compared with those of 52 inpatients who were previously treated with desipramine alone. The response to the desipramine plus fluoxetine combination was better than that obtained when desipramine was given alone. Weilburg et al. (1989) reported on the effects of fluoxetine added to an HCA. Improvement was seen in 86.7% of the patients. In all of the cases reported, the dose of the HCA was lowered after fluoxetine was added, due to the 2D6 inhibition. The HCA was discontinued for 12 of the 26 responders, of whom eight relapsed but recovered when the HCA was restarted. Levitt et al. completed a non-controlled study in which patients were treated with fluoxetine and imipramine (1999). 54% had a greater than 40% decrease in HDRS scores, and 31% of this group had a greater than 50% decrease in HDRS. Seth et al. examined eight cases of TRD treated with a combination of nortriptyline and a new SSRI, with or without concurrent lithium therapy (1992). Notable improvement was seen in all patients in whom other drug regimes, such as MAOIs, TCAs, neuroleptics and ECT, had been ineffective. Zajecka et al. reported on SSRI non-responders where an HCA was added to fluoxetine (1995). Their retrospective analysis demonstrated that 35% of subjects who demonstrated a partial response to fluoxetine responded fully when an HCA was added. Maes et al. completed a controlled study where monotherapy trazodone patients were randomized to receive placebo, pindolol or fluoxetine (1996). 72.5% of patients treated with trazodone plus pindolol, 75% of patients treated with trazodone plus fluoxetine, and 20% treated with trazodone plus placebo showed a clinically significant response. No unique adverse events were noted.

Dual serotonin-2 antagonists and reuptake inhibitors (Trazodone, Nefazodone)

Nefazodone and trazodone are novel agents with dual 5HT2 receptor antagonism and reuptake inhibition. Both act by potent blockade at the $5HT_{2A}$ receptor and weak serotonin reuptake inhibition. Nefazodone also has weak norepinephrine reuptake inhibition as well as weak alpha1-adrenergic-blocking properties. Trazodone contains $alpha_1$-antagonist properties, but lacks the norepinephrine reuptake inhibition (NRI) capability of nefazodone (Stahl et al. 2000). Both have antihistamine-1 receptor antagonism. Many of these properties are similar to mirtazapine (noted above) but also allow for a unique combination with NRI not known in other products. In many patients, trazodone produces sedation that can be poorly tolerated at therapeutic doses. It is for this reason that many clinicians choose to combine this drug in low doses (25-150 mg at bedtime) with other antidepressants as an off-label hypnotic. Trazodone can improve sleep onset and promote and normalize sleep architecture and, thus, theoretically reduce depressive symptoms associated with insomnia. In addition, the 5HT2 antagonism may produce anxiolytic effects as well as potential sexual dysfunction reversal associated with SSRIs. Apart from marked sedation, priapism is a side effect that the patient should be made aware of, and informed consent must be obtained from the patient before initiating treatment with trazodone.

Nefazodone is a unique antidepressant, but recent reports regarding its use are rare. Potential liver damage has resulted in a decline in its use in the United States. As seen in the case of trazodone, nefazodone's receptor profile with $5HT_2$ blockade can be quite helpful in reducing adverse effects such as sleep and sexual dysfunction associated with the use of SSRIs. If $5HT_2$ blockade is desired, safer alternatives include the use of mirtazapine or second-generation antipsychotics in low to moderate doses. In addition, the lack of antihistamine activity reduces the likelihood of sedation and increases the tolerability profile. Taylor and Prather completed a non-controlled study of nefazodone added to the patient's previous antidepressant regimen until an optimum response was achieved (2003). After adjunctive treatment, 63% achieved complete remission of depressive symptoms.

Conclusion

This paper serves as a review of how to manage patients with treatment resistant depression where monotherapy has failed to treat patients to remission. Polypharmacy may be the rule rather than the exception (Schwartz and Rashid 2007) when a clinician attempts to help a patient reach full remission of MDD symptoms, and is gaining popularity when side effects need to be alleviated in order for the patient to remain adherent to otherwise successful long-term medication management. It further illuminates for the reader where limited approvals regarding augmentation/combination exist, and further, how the astute psychopharmacologist must command knowledge of the off-label literature. Finally, readers must note that there are more open-label and anecdotal reports than controlled studies. There is often a dearth of stringent evidence base for certain medication combinations as the clinician strives to obtain the ideal remission of symptoms. When needed stringent data is unavailable, clinicians are advised to rely on knowledge of the drug's mechanism of action, and select rational polypharmacy approaches where non-overlapping pharmacodynamic properties may successfully address and ameliorate residual symptoms. All of the above must be carefully weighed against risk-benefit and cost-benefit analyses.

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