Depression with Anxiety: Optimizing Treatment with Pharmacogenetics

Alan F. Schatzberg, MD, Kenneth T. Norris, Jr, Professor of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, CA

Background: “mixed anxiety and depression” (composed of sub-syndromal manifestations of each symptom) eliminated from Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition); studies showed patients given that diagnosis typically had depression plus mild anxiety or had severe anxiety (eg, generalized anxiety disorder, panic disorder, posttraumatic stress disorder) plus comorbid depression; significant anxiety symptoms occur in 50% of patients with major depressive disorder (MDD), even if most do not meet criteria for comorbid anxiety; anxiety appears to predict poorer responses to treatment for depression, even though many medications used for depression (eg, selective serotonin reuptake inhibitors [SSRIs]) have also been approved for anxiety disorders

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al, 2006): citalopram alone showed remission rate of 30% and response rate of 45%; only 22% of patients with co-occurring anxiety symptoms showed remission, vs 33% of nonanxious patients; >50% of participants had significant anxiety; phase II—regardless of whether patients chose to switch or augment medications, significant anxiety associated with extremely low remission rates (6%-8%; vs 30% in patients with less anxiety); augmentation with benzodiazepines (BZDs) or atypical antipsychotics (AAPs) not included in study

International Study to Predict Optimized Treatment for Depression (iSPOT-D; Williams et al, phase I results, 2011): designed to use standardized assessments that may be explored for biomarkers (including pharmacogenetics); uses variety of software to incorporate, eg, electroencephalography, reaction time, high rate variability, cognition, and emotional processing; treatment-naive patients randomized to receive escitalopram (Lexapro; 10 mg), sertraline (Zoloft; 50 mg), or venlafaxine (Effexor; 75 mg), with option to increase to full recommended dose; iSPOT-D had higher remission rates than STAR*D (45%), with escitalopram showing slight superiority to other agents (possibly due to greater use of therapeutic doses); patients could request occasional BZD, but only 3% opted to; self-reporting showed far greater reductions in depression (compared to anxiety) with all medications; although anxiety strongly predicted poorer responses, categorizing patients based on type of depression (eg, atypical vs nonatypical, anxious vs nonanxious) not significantly predictive; patients with anxiety showed some response but had much lower rates of remission, greater impairments, and residual insomnia; speaker argues patients with this type of anxiety represent large number of refractory subjects seen in clinical practice

Treating residual anxiety: STAR*D showed adding buspiron et or buspiron to SSRI lacks efficacy; speaker argues treatment must go beyond monotherapy with antidepressants; approaches supported by prospective data—AAPs (particularly more calming agents; quetiapine has best data); BZDs (eg, clonazepam); mirtazapine (alone or in combination; effects similar to AAPs); ketamine (based on preliminary data)

Bandelow et al (2014): 300 mg of quetiapine significantly reduced anxiety in group of patients with high levels of anxiety, but 150 mg did not separate from placebo; 300 and 150 mg doses were effective in patients who had MDD without significant anxiety

Papakostas et al (2010): reanalysis of study wherein augmentation with clonazepam was compared to placebo in patients already receiving fluoxetine; at 3 wk, clonazepam was significantly superior to placebo

Mirtazapine (Remeron): available as generic; postsynaptic antagonist of serotonin 2 and serotonin 3 receptors; α2 receptor antagonist (causes release of norepinephrine, plus probable release of serotonin via interneurons); serotonergic affinities provide greater calming, and counteract gastrointestinal stimulation seen with SSRIs (thus negating nausea and diarrhea)

Schatzberg et al (2002): mirtazapine performed better than paroxetine in geriatric patients, particularly when measuring anxiety and sleep disturbances; although mirtazapine tends to cause
Niciu, Ionescu, et al (2014): in analysis of data from the National Institute of Mental Health, individuals with anxiety seemed to derive greater benefits from ketamine and maintained more of their response (relative to nonanxious patients)

**Pharmacogenetics**

**Background:** speaker does not particularly recommend pharmacogenetic testing, because of lack of prospective data demonstrating favorable cost-benefit ratio; in trials, testing tends to predict side effects better than responses; although pharmacogenetics can predict pharmacodynamic effects (effect at receptor), they have limited ability to predict which medications work in individual patients; conservative dosing can often achieve same outcomes as pharmacogenetic tests costing ≤$3000 USD

**Types of pharmacogenetic testing:** pharmacokinetics — genetic tests can predict slower metabolism of specific medications (thus predicting higher blood levels, which may cause toxicity); pharmacodynamics — some patients have alterations at, eg, serotonin receptor or reuptake sites, which can cause nausea or agitation in response to medications affecting sites; transport of medication into or out from brain — potentially more important than testing, eg, liver effects

Schatzberg AF et al (2002), pharmacologic aspects: mirtazapine and paroxetine act as substrates of cytochrome P-450 (CYP)2D6 enzyme; paroxetine also inhibits it (converting marginally adequate metabolizers into slow metabolizers); genotyping patients before prescribing these agents failed to predict either responses or side effects; serotonin transporter promoter — regulates uptake of serotonin into presynaptic neurons; predictor of risk for depression in response to stressors (eg, abuse, loss of parent in early childhood); patients with long (more common) variant of encoding gene tend to have better responses to SSRIs, while patients with short variant tend to have greater side effects; study found these variants failed to predict efficacy of medications but predicted discontinuation; serotonin 2a (postsynaptic) receptor — patients with CC genotype in polymorphism affecting this receptor showed high rates (>50%) of discontinuation on paroxetine, but not mirtazapine; regression analysis — genotyping of serotonin transporter and 2a receptor variants served as independent predictors, and thus when combined could predict discontinuation in 80% of patients receiving paroxetine

**P-glycoprotein (P-gp) pump:** affects transport of molecules into and out of brain; controlled by ABCB1 gene; allows cancer cells to rapidly pump out chemotherapeutic agents, preventing intended effects; controls blood-brain-barrier; patients who inherit certain forms of ABCB1 rapidly pump antidepressants out from their brain faster than medication can accumulate (explaining nonresponses); study (Uhr et al, 2003) — mice with knocked-out ABCB1 gene show significantly higher levels of citalopram in brain after dosing; serves as predictor only for antidepressants acting as substrates of P-gp; speaker’s study replicated previous data, showing P-gp variant predicted remission rates of 80% with paroxetine (but did not predict responses to mirtazapine); study (Ray et al, 2015) — patients carrying minor alleles on rs2235040 (seen in 10% of participants) showed response rates of 80% when given SSRIs (vs 40% with other alleles), plus fewer side effects (probably due to greater tolerance, decreased need to advance dose, and greater accumulation in brain with less accumulation in gut); thus, P-gp polymorphisms may effectively predict treatment responses and side effects

**Suggested Reading**


**Novel Agents for Treatment-Resistant Depression**

**Charles DeBattista, MD, DMH, Professor of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, CA**

**Ketamine:** glutamate most common excitatory neurotransmitter; observation of efficacy of glutamatergic agents in depression dates back to 1959, when D-cycloserine showed positive effects; first trials of ketamine for depression occurred >15 yr ago; more recently, NIMH began to systematically assess ketamine for treatment-resistant bipolar depression (Zarate et al, 2012); studies ongoing; appears to have rapidly acting effect (probably due to effect of N-methyl-D-aspartate antagonism on fast sodium-ion channels), occurring within 1 to 2 hr of dosing; ketamine-based strategies could be extremely beneficial for, eg, patients admitted to emergency departments due to suicidality or suicide attempts

**Issues with ketamine:** long history of use in chronic pain; known analgesic properties; concern about whether ketamine primarily acts as opiate (rather than glutamate-specific agent); if opiate hypothesis proven, clinical acceptance might change; psychotomimetic effects — doses used for depression may result in dissociation and depersonalization (typically transient); however, patients who use high doses on long-term basis can develop psychotic symptoms that may persist after discontinuation; lack of sustained benefits — literature suggests single dose (typically 0.5 mg/kg infused over 40 min) has benefits lasting 1 wk; studies design — since patients can often guess whether they have received ketamine, early efforts at controlled trials may have been biased; however, NIMH trials using midazolam (Versed) for comparison have indicated patients derive greater benefits from ketamine (Murrough et al, 2013)

**Sustaining benefits of ketamine:** repeated infusions — criticized as impractical, since patients may need weekly doses on indefinite basis (preferably under supervision of anesthesiologist); rapastinel (GLYX-13) — used in intravenous (IV) and oral formulations; phase II and III trials show positive data, albeit with U-shaped responsive curve; single dose shows sustained benefits; glutamate-specific agent that has reached furthest stage of development, and speaker speculate approval may occur ≤24 mo; D-cycloserine — higher doses (comparable to those recommended for TB) seemed to show efficacy in study of 13 patients (Kantrowitz et al, 2015); relatively inexpensive; safe as long-term treatment (patients with TB typically receive it for >2 yr)

**Intravenous scopolamine:** antagonist of muscarinic acetylcholine receptors; evidence suggests subset of patients develop depression while using muscarinic agonists (eg, physostigmine); likewise, some patients report rapid benefits for depression after significant dose of IV scopolamine; study (Drevets et al, 2013) — single 4 µg/kg dose given over 15 min yielded 32%
Vilazodone (Viibryd): harnesses direct feedback loop existing between facial expressions and brain; multiple studies suggest perceptions can be altered by forcing changes in facial expressions; eg, having individual hold pencil between their lips (thereby forcing them to smile) changes their perception of certain stimuli (including happy and sad faces); researchers theorize depression induces changes in facial expression, and those facial expressions feed back to brain and alter perception; based on this, investigators compared glabellar injections of botulinum toxin (approved for cosmetic use) to saline injections in patients with depression; study (Wollmer et al, 2012)—patients receiving toxin showed significant differences, which gradually increased over time and persisted for ≤54 mo; however, study may have been biased by inadequate blinding and controls (since paralytic effects of botulinum toxin appear obvious)

Psilocybin: increased abuse in 1960s derailed avenues of research; small studies published in reputable journals have suggested single doses might have long-term benefits; study (Grob et al, 2011)—patients with terminal cancer plus anxiety received single dose; significant and sustained benefits in anxiety and depression measures lasted for 6 mo of follow-up; speaker’s thoughts—not currently reasonable to try with patients; however, subset of patients may benefit from hallucinogens; “spiritual insights” associated with psilocybin have produced long-term benefits, as well as long-term problems (eg, flashbacks); however, problematic effects often associated with more aggressive use

Vilazodone (Viibryd): may offer superior tolerability (particularly regarding sexual side effects) to other SSRIs; reasonably effective anxiolytic; not especially potent but effective in some patients

Melatonergic agents: melatonin (over-the-counter) and ramelteon do not appear beneficial in depression; agomelatine—agonist of M1 and M2 receptors, and antagonist of serotonin 2c receptor; approved in Europe for several years; associated with dose-related hepatotoxicity in small percentage of patients; beneficial to sleep; negligible sexual side effects; highly effective in subset of patients unresponsive to other agents

Vortioxetine: serotonergic agent with complex effects; shows interesting cognitive benefits, which occur independently of antidepressant effects; approved in several European countries as first cognitive enhancing agent for depression (application for approval in US ongoing); speaker views cognitive issues as most concerning aspect of depression, because they appear to accumulate over time; studies suggest each recurrence of depression may be associated with 2% to 3% decrement in memory function, which does not improve; depression has been identified as second leading modifiable risk factor for development of Alzheimer disease, and causes changes in brain areas that may predispose individuals to cognitive difficulties (possibly throughout life)

Triple reuptake blockers: no agents currently on market; block reuptake of dopamine, serotonin, and norepinephrine in relatively balanced way; older dopamine reuptake blockers associated with problems (eg, hepatoxicity) and taken off market, but offered unique benefits (eg, limited sexual side effects, rapid efficacy, appetite suppression)

Buprenorphine: currently under evaluation for depression; combination with μ-opioid antagonist significantly decreases risk for abuse; phase II trials showed impressive results; Food and Drug Administration has indicated combination might receive approval in 2016

Suggested Reading


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1. When attempting to augment a patient’s antidepressants to address residual anxiety, which of these atypical antipsychotic medications is supported by the strongest evidence?
   (A) Aripiprazole  (B) Ziprasidone  (C) Quetiapine  (D) Olanzapine

2. Which of these medications has the ability to counteract gastrointestinal side effects associated with selective serotonin reuptake inhibitors?
   (A) Quetiapine  (B) Ziprasidone  (C) Mirtazapine  (D) Clonazepam

3. In a study analyzing data from the National Institute of Mental Health, ketamine appears to yield more significant benefits and longer-lasting responses in patients with which of the following characteristics?
   (A) Depression with anxiety  (B) Depression without anxiety  (C) Atypical depression

4. Which of the following is associated with genetic polymorphisms that can predict the development of depression in response to major early-life stressors?
   (A) Cytochrome P-450 2D6 enzyme  (B) Serotonin transporter promoter  (C) Postsynaptic serotonin 2a receptor  (D) P-glycoprotein

5. Which of the following affects the transport of molecules across the blood-brain-barrier and, in patients with certain genetic polymorphisms, causes some antidepressants to be removed from the brain faster than they can accumulate?
   (A) Cytochrome P-450 2D6 enzyme  (B) Serotonin transporter promoter  (C) Postsynaptic serotonin 2a receptor  (D) P-glycoprotein

6. Which of these approved and currently available agents has shown the greatest potential in helping to sustain the effects of ketamine?
   (A) Riluzole  (B) Memantine  (C) D-cycloserine  (D) Buprenorphine

7. Which of the following agents appears to produce antidepressive effects through antagonism of the muscarinic acetylcholine receptor?
   (A) Scopolamine  (B) Physostigmine  (C) Botulinum toxin  (D) Psilocybin

8. Which of these antidepressants has unique effects at melatonin receptors, and thus is beneficial to sleep?
   (A) Ramelteon  (B) Agomelatine  (C) Vortioxetine  (D) Edivoxetine

9. Which of the following agents is the only antidepressant yet shown to improve the cognitive aspects of depression?
   (A) Rapastinel (GLYX-13)  (B) Esketamine  (C) Vilazodone  (D) Vortioxetine

10. The Food and Drug Administration has indicated it may be prepared to approve buprenorphine for depression, although only in combination with which of the following types of agents?
    (A) Selective serotonin reuptake inhibitor  (C) Glutamate antagonist  (B) Serotonin-norepinephrine reuptake inhibitor  (D) μ-opioid antagonist

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