

PSYCHIATRY DRUG ALERTS

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Brexanolone Infusion for Postpartum Depression

The FDA has approved brexanolone injection (*Zulresso*) for intravenous use in the treatment of postpartum depression (PPD). This represents the first agent specifically approved for PPD.

Zulresso is administered as a continuous IV infusion over 2.5 days. Due to risk of excessive sedation and sudden loss of consciousness, the drug will only be available through a Risk Evaluation and Mitigation Strategy (REMS) program with restricted distribution. During infusion, women must be monitored for excessive sedation and sudden loss of consciousness, have continuous pulse oximetry monitoring, and must be accompanied during interactions with their child(ren). Patients should be advised not to drive, operate machinery, or engage in other dangerous activities until feelings of sleepiness from the treatment have completely abated.

FDA News Release: FDA approves first treatment for post-partum depression. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm633919.htm.

Buprenorphine–Naloxone for PTSD

Veterans with PTSD who received treatment with buprenorphine–naloxone (*Suboxone*) had fewer symptoms and greater improvement than those taking an SSRI, according to a retrospective study.¹ The effects were modest but may be clinically significant enough to encourage randomized trials of buprenorphine for treatment of PTSD. Currently, SSRIs are recommended as the core pharmacotherapy for the disorder but produce remission in less than one-third of patients.

Methods: This retrospective chart review was conducted in patients treated at a single VA medical center. Study subjects had a diagnosis of PTSD and had ≥ 2 symptom scores available on the PTSD Checklist for Clinicians (PCL-C) or the VA Primary Care PTSD Screen (PC-PTSD). Patients were receiving an SSRI, prescription opioids (for pain), or buprenorphine–naloxone, but not >1 of these medications. The primary study outcome was the mean final standardized PTSD score on either of the scales.

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Results: A total of 2015 patients were identified for inclusion in the study, the large majority taking SSRIs. The final sample consisted of 55 randomly selected patients in each of the 3 medication groups. Three-fourths were white, 89% were men, and the average age was 43 years. Patients had been taking their study medication for >2 years on average.

Patients receiving buprenorphine–naloxone had significantly lower final PTSD symptom scores than those taking SSRIs ($p=0.048$). In other pairwise comparisons, opioids did not differ from buprenorphine–naloxone or SSRIs. Change from baseline in PTSD symptoms, a secondary outcome, also favored buprenorphine–naloxone in comparison to SSRIs ($p=0.026$). Symptom scores decreased by 24% with buprenorphine–naloxone and 16% with opioids; scores increased slightly with SSRIs.

Discussion: Many patients with PTSD self-medicate with opioids. The kappa opioid receptor may represent an important pharmacological target in PTSD. Buprenorphine is also active at both mu and kappa opioid receptors and could be a novel treatment for PTSD symptoms. Results of the present study are consistent with another recently published retrospective study² comparing buprenorphine–naloxone with opioids. However, they must be interpreted cautiously, as confounding factors (e.g., age, comorbidity, participation in psychotherapy) were not addressed.

¹Lake E, Mitchell B, Shorter D, Kosten T, et al: Buprenorphine for the treatment of posttraumatic stress disorder. *The American Journal on Addictions* 2019; doi 10.1111/ajad.12860. From Central Arkansas Veterans Healthcare System, North Little Rock; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

²Seal K, et al: Observational evidence for buprenorphine's impact on posttraumatic stress symptoms in veterans with chronic pain and opioid use disorder. *Journal of Clinical Psychiatry* 2016;77:1182.

Brain Zaps During Antidepressant Discontinuation

Sensations perceived as electrical flashes that occur in the brain, often described by patients as "brain zaps", are a poorly understood symptom of antidepressant discontinuation. The causal mechanism of brain zaps is unknown, but they appear to be related in part to how rapidly antidepressant activity diminishes in the brain after discontinuation.

Information on brain zaps spontaneously reported by patients on the Mental Health Daily website, a discussion forum for mental-health issues, was used in an effort to characterize the experience and circumstances surrounding the phenomenon. Over a 2-year period, 378 posts were identified describing brain zaps associated with taking antidepressants. Venlafaxine accounted for about one fourth of these occurrences, disproportionate to its prescribing frequency. Fluoxetine, 1 of the most often prescribed antidepressants, accounted for only 3% of the posts. Sertraline, escitalopram, and duloxetine were reported roughly in proportion to their prescribing frequency. Brain zaps were most often reported after abruptly stopping (40%) or tapering (26%) the antidepressant. A total of 37% of patients experienced these symptoms for a month or less, and three fourths for less than a year, but a small minority of patients reported experiencing them for 5–39 years.

The sensations were reported as an electric shock within the skull, sometimes accompanied by dissociation, vertigo, and a buzzing sound. Eye movements were sometimes reported as a trigger. A minority of patients reported the zaps as pleasurable or at least preferable to depressive symptoms, most reported no or minor negative impact, and a few described interference with usual activities and even suicidal thoughts. Patients used nearly 50 methods to attempt to get relief from the symptoms, such as exercise, relaxation, and various supplements; none seemed effective.

Although this group is a convenience sample, it is similar to other groups of antidepressant users in whom antidepressant discontinuation syndromes have occurred. While the collected

data are not suitable for statistical analysis, it does demonstrate trends that could be used to further investigate the phenomenon of antidepressant-discontinuation brain zaps.

Papp A, Onton J: Brain zaps: an underappreciated symptom of antidepressant discontinuation. *Primary Care Companion for CNS Disorders* 2018; doi 10.4088/PCC.18m02311. From the University of California, San Diego. **This study was not funded. The authors declared no competing interests.**

Common Drug Trade Names: duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

Psychotropic/Antiretroviral Interactions: Substance Abuse Treatments

Substance use disorders are an important concern in patients with HIV. Intravenous drug use is a significant risk factor for the acquisition of HIV, and alcohol use disorders negatively impact overall physical health, particularly through a heightened risk of liver dysfunction and damage. Both conditions negatively affect adherence to antiretroviral therapies (ART) in patients with HIV, and pharmacokinetic and compounding adverse effects are possible.

Methadone metabolism involves multiple CYP isoenzymes, with CYP2B6 playing the largest role, followed by 3A4. Clinically significant interactions between methadone and most integrase strand transfer inhibitors (INSTIs), protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase inhibitors (NRTIs) are uncommon. There are however, individual agents within each class of ART medication that affect methadone metabolism. (See table.) In addition, methadone has been shown to reduce concentrations of the NRTIs didanosine and stavudine and to increase zidovudine exposure.

Interactions between ART regimens and methadone			
Agent(s)	ART Class	Interaction	Recommendations
Elvitegravir	INSTI	Because elvitegravir can only be administered with the CYP3A4 inhibitor cobicistat, there is a theoretical concern for an interaction with methadone.	Limited evidence suggests the combination can be used without need for dosage adjustments.
Nelfinavir	PI	Coadministration can reduce methadone concentrations by up to 50%; opioid withdrawal is uncommon but may occur.	Dose adjustment is not usually required, but patients should be monitored for signs of opioid withdrawal.
Ritonavir	PI	Boosting a PI with ritonavir lowers methadone concentrations.	While dosage adjustments are not necessarily required, patients should be monitored for symptoms of opioid withdrawal and the methadone dose increased if needed.
Efavirenz and nevirapine	NNRTIs	Because of their CYP2B6 inducing action, opioid withdrawal occurs frequently when either agent is coadministered with methadone.	Guidelines recommend increasing methadone doses when using this combination as well as close monitoring for ≥ 2 weeks as the onset of the interaction may be delayed.
Abacavir	NRTI	Coadministration produces a minor increase in methadone clearance.	Dosage adjustment is not required.

In patients receiving treatment with buprenorphine for opioid dependence, ART regimens including ritonavir produce a significant increase in buprenorphine plasma levels and raise the risk of buprenorphine toxicity. In addition, patients administered buprenorphine with unboosted atazanavir may experience increased sedation and reversible elevations in total bilirubin. Guidelines recommend against coadministration of buprenorphine with unboosted atazanavir and close monitoring of those receiving buprenorphine with ritonavir. When patients receiving a PI or the INSTI elvitegravir require buprenorphine treatment, it should be started at the lowest initial dose and titrated carefully.

There are 4 agents FDA-approved to maintain abstinence in alcohol use disorders: acamprosate, disulfiram, oral naltrexone, and intramuscular naltrexone. None of these agents have significant CYP effects, and coadministration with ART regimens is generally considered to be safe. However, coadministration of atazanavir has been shown to negate the efficacy of disulfiram, and the combination should be avoided. In addition, the lopinavir–ritonavir combination product contains ethanol, and coadministration with disulfiram could lead to a disulfiram-like reaction, which causes vomiting, flushing, diaphoresis, and palpitations, and may be severe enough to cause respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, or acute congestive heart failure.

In addition to the pharmacokinetic interactions described, concurrent use of substance use disorder medications and ART regimens can have compounding effects. Across the classes, multiple agents (e.g., methadone, buprenorphine, PIs, disulfiram, naltrexone) have been associated with elevations in liver enzyme levels and hepatotoxicity, which may be particularly concerning in the presence of alcohol-associated liver disease. QT prolongation has also been reported with many agents used to treat these disorders. Concurrent use of multiple QT prolonging medications could have additive effects. Finally, adverse effects that are common with many of these agents include hypotension, constipation, nausea, vomiting, dizziness, sedation, diaphoresis, insomnia, loss of appetite, and increased creatinine kinase levels. Combining multiple agents that cause these effects could increase the likelihood of occurrence as well as severity of symptoms.

Editor’s Note. This is the final report in a 5-part series on psychotropic/antiretroviral interactions. We previously covered interactions with antidepressants, stimulants, antipsychotics, and anxiolytics and mood stabilizers. (See November 2018 through February 2019 issues.)

Goodlet K, Zmarlicka M, Peckham A: Drug-drug interactions and clinical considerations with co-administration of antiretrovirals and psychotropic drugs. *CNS Spectrums* 2018; doi 10.1017/S109285291800113X. From Midwestern University College of Pharmacy, Glendale, AZ; and other institutions. **Source of funding not stated. Two of 3 study authors disclosed potentially relevant relationships; the remaining author declared no competing interests.**

Common Drug Trade Names: abacavir—*Ziagen*; acamprosate—*Campral*; atazanavir—*Reyataz*; buprenorphine—*Belbuca*, *Probuphine*; cobicistat—*Tybost*; didanosine—*Videx*; disulfiram—*Antabuse*; efavirenz—*Sustiva*; elvitegravir (no longer available as a stand-alone product in the U.S.)—*Stribild*, *Vitekta*; lopinavir–ritonavir—*Kaletra*; naltrexone, intramuscular—*Vivitrol*; nelfinavir—*Viracept*; nevirapine—*Viramune*; ritonavir—*Norvir*; stavudine—*Zerit*; zidovudine—*Retrovir*

Injectable Naltrexone for Opioid Use Disorder

In a preliminary randomized trial, patients with opioid use disorder who received injectable naltrexone were twice as likely to remain in treatment following inpatient detoxification than those who received oral naltrexone.

Methods: Study subjects were adults seeking treatment for opioid dependence. After undergoing a week-long inpatient program of medication-assisted opioid detoxification and naltrexone induction, they were randomly assigned to 50 mg/day open-label oral naltrexone for 24 weeks or monthly IM injections of 380 mg XR naltrexone (*Vivitrol*) for a total of 6 injections. Ongoing naltrexone treatment was started before discharge. Patients were seen in the clinic 3

times per week for the first 2 weeks, then twice a week for the remainder of the study. During these visits they received behavioral naltrexone therapy, a treatment developed at the clinic to support adherence to oral naltrexone and adapted for this study to support oral or injectable forms. The primary outcome of the randomized trial was retention in treatment.

Results: Of 608 persons screened for the study, 110 consented and entered inpatient treatment. Of these, 60 either successfully completed detoxification or were already abstinent at study entry and were randomly assigned to oral or injected naltrexone. Patients were predominantly male, in their late 30s on average, and white. Of 35 patients who did not complete the trial, 19 were nonadherent with attendance, 5 were nonadherent with study medication, 5 relapsed to opioid use while still attending sessions, 4 withdrew for adverse events, and 2 withdrew consent.

The time to treatment dropout was significantly longer among patients receiving extended-release naltrexone than oral naltrexone (adjusted hazard ratio,* 2.18; see table). The percentage of opioid-positive urine tests was 2.4% in the XR naltrexone group and 8.8% in the oral naltrexone group, a statistically nonsignificant difference. Patients in the XR group attended a mean of 17 therapy sessions, compared with 12 sessions in the oral naltrexone group.

Rates of retention in treatment for opioid use disorder			
	4 weeks	12 weeks	24 weeks
Oral naltrexone	62.5%	43.8%	28.1%
Injectable XR naltrexone	85.7%	60.7%	57.1%

Most of the adverse events in the study were consistent with opioid withdrawal. A single patient was withdrawn from the study after an apparent skin reaction to injected naltrexone; 1 was withdrawn during naltrexone induction but prior to randomization because of severe hypotension; and 1 in the XR naltrexone group was withdrawn after developing increased anxiety and alcohol use.

Discussion: The generalizability of these results is limited to highly motivated, treatment-seeking patients. Although rates of treatment failure were high, patients who received IM naltrexone remained in treatment longer than those who received the oral formulation, possibly suggesting that the IM formulation should not be reserved for patients who undergo a failed trial of oral naltrexone.

Sullivan M, Bisaga A, Pavlicova M, Carpenter K, et al: A randomized trial comparing extended-release injectable suspension and oral naltrexone, both combined with behavioral therapy, for the treatment of opioid use disorder. *American Journal of Psychiatry* 2019;176 (February):129–137. doi 10.1176/appi.ajp.2018.17070732. From Columbia University and New York State Psychiatric Institute, New York; and Alkermes, Waltham, MA. **Funded by the National Institute on Drug Abuse. Four of 9 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Pharmacotherapy for Generalized Anxiety Disorder

According to the results of a network meta-analysis,* evidence supports venlafaxine, pregabalin, escitalopram, and duloxetine as first-line pharmacotherapy for generalized anxiety disorder.

Methods: Randomized controlled trials, conference abstracts, trial summaries published by sponsors, and regulatory documents describing comparisons of ≥ 2 commercially available medications or placebo in patients with generalized anxiety disorder were identified in the literature. Studies that included patients with major comorbidities other than depression and those that examined discontinuation strategies or relapse prevention were not included in the analysis.

Results: A total of 89 studies, with 25,441 participants and investigating 22 active medications, met inclusion criteria. Trial durations ranged from 4 to 26 weeks, with a median duration of 8

weeks, and all used the Hamilton Rating Scale for Anxiety (HAM-A) as the primary or a secondary efficacy outcome (median baseline HAM-A score, 25). A total of 63 trials were placebo controlled, and 45 compared multiple active drugs. Most of the trials were conducted by pharmaceutical companies as part of a clinical development program.

For most of the drugs, efficacy was superior to placebo and acceptability, which was measured as the rate of premature withdrawal, was similar to placebo. Among the agents investigated, quetiapine had the largest effect on the HAM-A (see table), but patients who received quetiapine were less likely to complete treatment than those receiving placebo. Duloxetine, pregabalin, venlafaxine, and escitalopram were also found to be effective without an elevated rate of discontinuation. (See table.) Several other agents showed promising efficacy but with limited sample sizes—notably sertraline, fluoxetine, bupropion, and buspirone. Paroxetine and benzodiazepines showed promising efficacy but had elevated rates of discontinuation. Of the newer agents, only agomelatine (not available in the U.S.) showed promising efficacy and acceptability, although with a small sample size. Vortioxetine and vilazodone did not appear to be effective.

Efficacy and acceptability of active medication vs placebo for generalized anxiety disorder			
Drug (ranked by efficacy)	Number of trials	Efficacy—Mean change from baseline in HAM-A	Tolerability—Odds of premature discontinuation
Quetiapine	4	-3.60	1.44
Duloxetine	8	-3.13	1.09
Pregabalin	11	-2.79	0.80
Venlafaxine	14	-2.69	0.98
Escitalopram	13	-2.45	0.96

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Slee A, Nazareth I, Bonda, Liu Y, et al: Pharmacological treatments for generalised anxiety disorder; a systematic review and network meta-analysis. *Lancet* 2019; doi 10.1016/S0140-6736(18)31793-8. From University College London, U.K.; and the University College of Wales, Cardiff, U.K. **This analysis was conducted without funding. Two of 6 authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: bupropion—*Wellbutrin*; buspirone—*BuSpar*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine—*Paxil*; pregabalin—*Lyrica*; quetiapine—*Seroquel*; sertraline—*Zoloft*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Trintellix*

*See Reference Guide.

Adjunctive Medications in Schizophrenia

In an observational study of patients taking a second-generation antipsychotic and requiring adjunctive medication, adding an antidepressant was associated with better outcomes than adding an alternative psychotropic medication. Poorer outcomes occurred in patients adding a benzodiazepine or mood stabilizer, and use of these agents warrants clinical caution.

Methods: The study examined outcomes in a cohort of patients (n=81,921; 46% women) covered by Medicaid—the insurer for most patients with schizophrenia in the U.S.—over a 10-year period. Study subjects were adults, aged 18–64 years, with schizophrenia who were receiving treatment with a second-generation antipsychotic as monotherapy for ≥90 days, and then initiated a single new psychotropic medication. Adjunctive medications evaluated were another second generation antipsychotic (the reference category; n=26,014), an antidepressant (n=31,117), a mood stabilizer (n=12,849), or a benzodiazepine (n=11,941). Patients taking clozapine, as either an initial or an adjunctive medication, were excluded from the analysis. Propensity score matching* was used to balance the characteristics of patient groups receiving the 4 medication choices, and the primary study outcome was time to psychiatric hospitalization. Secondary outcomes included psychiatric emergency department visits, self-injury, mortality, and medical outcomes.

Results: Patients who added an antidepressant had a lower risk of hospitalization than those starting a second antipsychotic (hazard ratio [HR],* 0.84). Risk of hospitalization was increased after adding a benzodiazepine (HR, 1.08). The rate of hospitalization was not increased significantly in patients starting a mood stabilizer, but these agents were associated with increased mortality (HR, 1.31). This unexpected finding led the authors to examine individual mood stabilizers. Gabapentin accounted for 14% of mood-stabilizer initiations and 28% of deaths. No other mood stabilizer was associated with increased mortality. Mortality was also increased in patients after adding a benzodiazepine (HR, 1.22).

Compared with adding a second antipsychotic, starting an antidepressant was associated with a lower risk of psychiatric emergency department visits (HR, 0.92), and benzodiazepines with a higher risk (HR, 1.12). Compared with initiating an antipsychotic, antidepressants were associated with reduced risk of diabetes (HR, 0.87). No treatment strategy differed from others in the risk of self-injury.

Discussion: Antipsychotic monotherapy is often insufficient in patients with schizophrenia, and switching to an alternate antipsychotic or adding another class of psychotropic medication are common treatment strategies. However, little high-quality evidence supports the effectiveness of these approaches. The present results suggest that adding an antidepressant may be a better option than adding a benzodiazepine or mood stabilizer.

The authors note that because the study data do not include information on what prompted the medication changes, it is possible that clinical characteristics (e.g., refractory illness, comorbid anxiety) affected the choice of adjunctive treatment. While a large number of covariates were included in the propensity scoring process, residual confounding by unmeasured variables remains possible.

Stroup T, Gerhard T, Crystal S, Huang C, et al: Comparative effectiveness of adjunctive psychotropic medications in patients with schizophrenia. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2018.4489. From Columbia University Irving Medical Center, New York; and other institutions. **Funded by the Patient-Centered Outcomes Research Institute. Three of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: clozapine—*Clozaril*; gabapentin—*Neurontin*

*See Reference Guide.

Breakthrough Symptoms with LAI Antipsychotics

Despite the advantages of long-acting injectable antipsychotics in providing consistent medication exposure, patients may experience breakthrough symptoms. The literature contains very little evidence or guidance for clinicians regarding the management of patients who experience breakthrough symptoms or who become acutely ill while receiving LAI agents.¹

Low plasma drug levels may contribute to breakthrough psychosis. Therapeutic plasma reference ranges for LAI antipsychotics have been published.² Although preliminary (they are based on oral formulations), these levels can be used with therapeutic dose monitoring to guide dosing decision making. (See table, next page.) Depending on their onset of action, LAI antipsychotics require supplementation with oral doses for variable periods until steady-state therapeutic levels are reached. Drug-drug interactions can cause symptom breakthrough or worsening; for example, carbamazepine can decrease concentrations of aripiprazole, risperidone, or olanzapine.

When patients receiving LAI antipsychotics experience breakthrough symptoms, it is important to determine the cause of the exacerbation. Breakthrough symptoms may be the result of psychotic relapse, concurrent medical illness, substance use, psychiatric comorbidity, stressors, or nonadherence to treatment. To help alleviate psychotic symptoms, it may be possible to give the next dose early, increase the dose, or shorten the dosing interval. The proper administration

technique for LAI antipsychotics is essential and may require sufficient shaking, choosing the appropriate needle size and administration site, injecting into the muscle, and rapid injection without hesitation.

LAI antipsychotics: general recommendations based on therapeutic dose monitoring				
Efficacy	Adverse effects	Serum concentration reference range		
		Low	In Range	High
Good	None or mild	Continue	Continue	Continue
	Moderate or severe	Change [±]	Decrease dose	Decrease dose
Poor	None or mild	Increase dose	Increase dose	Change
	Moderate or severe	Change	Change	Change

[±]Change to a different medication

If symptoms remain after potential problems have been addressed, the LAI can be supplemented with a low dose of an oral antipsychotic (same formulation as LAI is preferred) until symptoms resolve. Two weeks after initiation, the oral antipsychotic can be discontinued if it is effective. If oral supplementation is not effective, it can be increased to the maximum effective dose and the patient reevaluated after another 1–2 weeks. If symptoms still persist, the LAI dose may be increased, the dosing interval can be shortened, or the patient can be switched to an alternate LAI or oral agent. It is also important that medical and other possible contributors continue to be addressed.

¹Correll C, Sliwa J, Najarian D, Saklad S: Practical considerations for managing breakthrough psychosis and symptomatic worsening in patients with schizophrenia on long-acting injectable antipsychotics. *CNS Spectrums* 2018; doi 10.1017/S1092852918001098. From Hofstra Northwell School of Medicine, Hempstead, NY, and other institutions. **Funded by Janssen Scientific Affairs, LLC. All study authors disclosed potentially relevant financial relationships.**

²Hiemke C, Bergemann N, Clement H, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry* 2018;51:e1

Common Drug Trade Names: aripiprazole LAI—*Abilify Maintena, Aristada*; carbamazepine—*Tegretol*; olanzapine—*Zyprexa Relprevv*; risperidone LAI—*Risperdal Consta*

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Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Network Meta-Analysis: An analytic method that extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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