OLDER ANTIPSYCHOTICS/KETAMINE

Review of Older Antipsychotics

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Meta-analysis (Leucht et al, 2013): clozapine showed superior efficacy among 15 antipsychotic (AP) agents; efficacy of haloperidol ranked near median; olanzapine and risperidone seem to show slightly better-than-average efficacy, but confidence intervals (CIs) overlap; findings concur with other high-quality studies that have consistently failed to find evidence for superiority of newer APs; haloperidol particularly effective; chlorpromazine showed somewhat poorer efficacy (but again, CIs overlap)

Study (Tiihonen J et al, 2009): in survival probability and relapse rates, depot paliperidone and haloperidol virtually identical; consistent with other data indicating newer long-acting APs lack advantages over older long-acting APs

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Speaker’s overall conclusions from study data: clozapine stands out as most effective AP; risperidone and olanzapine may be slightly superior to other APs (although appearance of superiority probably relates to study design and dosing rather than intrinsic characteristics); simply dividing APs in categories of “newer” and “older” no longer appropriate

Maintenance treatment of psychosis with APs: ie, use of APs in stable patients to reduce risk and severity of relapses, and thus to improve efficacy of rehabilitation; study (Csernansky and Schuchart, 2002) — multicenter trial assessing relapse-free survival time; risperidone found slightly superior to haloperidol; findings consistent with multiple studies showing newer APs have advantage over older APs in maintenance treatment; this trend may relate to higher rates of side effects experienced with older APs (particularly akathisia and rigidity), and associated reductions in adherence; meta-analysis (Leucht et al, 2012) — in placebo-based comparisons, first-generation APs (FGAs) and SGAs had overlapping efficacy (with FGAs showing slight advantage); results may be attributed to increasing prevalence of placebo responses in recent studies

Speaker’s arguments against oral haloperidol: although clinical differences between haloperidol and risperidone small, assessments of side effects revealed patients felt much better on risperidone; speaker asserts this difference in patient experiences has not been sufficiently acknowledged, and that patients experience much less discomfort with SGAs (particularly compared to FGAs used at excessive doses)

Depot APs: should have fewer side effects than oral agents (when skillfully administered), due to association between maximum plasma concentration and emergence of side effects; patients on haloperidol decanoate tend to have relatively low plasma concentrations; study (McEvoy et al, 2014) — compared haloperidol decanoate to paliperidone palmitate in 311 patients; although no differences in efficacy found, paliperidone caused far greater weight gain (mean of 6 kg, compared with mean weight loss of 3.88 kg with haloperidol) through entire 24 mo of trial; no differences in incidence of extrapyramidal symptoms (EPS) found; paliperidone associated with significantly better scores on Barnes Akathisia Rating Scale, but haloperidol caused akathisia in only 10% of patients overall; paliperidone caused statistically significant increase in incidence of prolactin elevation, and although no differences in sexual side effects were found, women enrolled in study reported higher rates of breast enlargement, galactorrhea, and menstrual irregularities

Dosing: finding “sweet spot” more difficult with older APs; controversies have recently emerged over long-term safety of APs, as patients receiving higher doses have shown loss of gray matter (plus other related side effects); since multiple studies suggest these changes have clear relationship with dose, speaker emphasizes importance of using lowest dose possible in long-term treatment; study (Van Putten et al, 1990) — newly admitted patients with schizophrenia randomized to receive 5, 10, or 20 mg of haloperidol; 20 mg dose showed greatest efficacy, although all doses effective; however, 20 mg dose was associated with greater withdrawal-retardation scores on Brief Psychiatric Rating Scale (BPRS; probably related to EPS), plus higher rates of akinsia and withdrawal from study; thus, 20 mg dose has greatest efficacy only in minority of patients who can tolerate its effects; study (Marder et al, 1987) — patients on extremely low dose of long-acting AP (fluphenazine) slightly more vulnerable to relapse, but these represented mild worsening which was

Educational Objectives

The goals of this program are to improve the use of older antipsychotic (AP) medications and to improve clinicians’ ability to prescribe ketamine for treating depression. After hearing and assimilating this program, the clinician will be better able to:

1. Compare the rates of overall survival, remission, and adherence associated with older and newer AP medications.
2. Provide appropriate medications and dosages for maintenance treatment, and thus prevent relapse while promoting adherence in patients whose psychosis has entered remission.
3. Monitor patients for movement disorders, endocrine changes, and metabolic issues that may result from AP medications.
4. Describe the role of glutamate in the pathophysiology of depression and its relationship to the therapeutic effects of conventional antidepressants, electroconvulsive therapy, and ketamine.
5. Rapidly improve depression and suicidality with low-dose infusions of ketamine.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, the following has been disclosed: Dr. Marder is a consultant for AbbVie, Hoffmann-La Roche, H. Lundbeck A/S, Merck & Co, Otsuka, and Pfizer; and receives grant/research support from Sunovion. Dr. Paleos reported nothing to disclose. In his lecture, Dr. Paleos presents information related to the off-label or investigational use of a therapy, product, or device.
usually treatable with quick intervention; this suggests low doses can be effective if carefully monitored and adjusted.

Strategies for decreasing AP burden: prescribing low doses and supplementing when symptoms worsen; engaging in process of shared decision making with patients (eg, discussing advantages and disadvantages, lowering dose while empowering patient to seek help if they feel worse); intermittent treatment — ie, stopping AP and restarting when symptoms worsen; multiple studies have found this approach generally unsafe.

Managing side effects: compared to newer APs, side effect profiles of older APs most distinctly marked by higher rates of EPS and prolactin elevation; study (Leucht et al, 2013) — among 15 APs, incidence of EPS most substantial with haloperidol; speaker emphasizes importance of learning to carefully look for and measure even subtle EPS.

Brief clinical assessment of movement disorders: takes ≤ 2 min; look for restless movements (with patient sitting); ask about difficulty sitting still (most important question) and feelings of restlessness; since patients may not be accurate reporters, ask family member about, eg, pacing or difficulty sitting; watch for spontaneous movements and tremor; check for cogwheeling; assess patient’s walking for reduced arm swing (best evidence for mild rigidity); newer APs primarily cause mild EPS, which typically manifest as akathisia and slight rigidity; tardive dyskinesia — observe for abnormal movements while patient sitting flat and distracted withthumb tapping; observe for truncal and arm or hand movements while patient stands and walks.

Prolactin elevation: seems more strongly associated with risperidone and paliperidone than with haloperidol.; particularly important in younger patients because of sexual side effects; since aripiprazole can lower prolactin (only AP with this effect), small doses may be useful as adjunct in patients who respond well to paliperidone or risperidone but develop elevated prolactin; prolactinology — since dopamine normally inhibits prolactin-secreting cells, dopamine antagonists cause elevations in prolactin; ask women about changes in menstruation or libido, and spontaneous lactation; ask men about changes in sexual function; ask about restless movements (with patient sitting); ask about changes in arm and hand movements while patient stands and walks.

Metabolic problems: speaker emphasizes importance of aggressive interventions, and asserts these problems occur with all APs (not only newer agents); monitoring — critical; speaker argues monitoring cannot be left to medical practitioners alone; weight problems, type 2 diabetes, and hyperlipidemia often develop before patients have ever received APs; Mt Sinai recommendations — weigh patients before starting APs and during every office visit (at least for first 6 mo; patients can also be asked to weigh themselves, which empowers them to monitor and control side effects); measure fasting plasma glucose or hemoglobin A1c and triglycerides before and soon after starting AP (particularly with olanzapine, quetiapine, or clozapine).

Controlling weight gain: lifestyle interventions and exercise effective; metformin — efficacy supported by growing evidence; in many cases where changing AP does not affect insulin resistance, adding metformin (sometimes at doses ≥ 1000 mg) may help; data show patients who receive metformin lose weight, and metformin plus lifestyle changes increases this weight loss.

Suggested Reading:

Safety and Effectiveness of Ketamine
K. Casey Alexander Paleos, MD, Clinical Assistant Professor, Department of Psychiatry, New York University Langone School of Medicine, New York, NY.

Background: nearly all antidepressants discovered and currently in use exert effects via monoamine systems; limitations of conventional antipsychotics — delayed onset of effect (2-6 wk in ≥50% of patients, but may be ≤3 mo); high rates of resistance; speaker argues depression represents blanket term that encompasses heterogeneous underlying pathophysiologies that result in phenotype of depression.

Glutamate: primary excitatory neurotransmitter in central nervous systems (CNS) of mammals; binds to receptors ubiquitously expressed in CNS; role in depression increasingly supported by postmortem and preclinical data; serum and cerebrospinal fluid of patients with major depressive disorder (MDD) show increased levels of glutamate; postmortem samples taken from prefrontal cortices of patients with depression show reductions in glial cells (responsible for reuptake of glutamate), high levels of glutamate, and alterations in binding affinity and expression of N-Methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), 2 of 3 major types of glutamate receptors found in human neocortex; important in prefrontal cortex (significantly involved in pathophysiology of depression), superior temporal cortex, and medial temporal lobe.

Effects of conventional antidepressant therapies on glutamate systems: selective serotonin reuptake inhibitors, tricyclic antidepressants, and electroconvulsive therapy (ECT) cause delayed downregulation of NMDA receptors (occurs after 10-14 days with imipramine and citalopram, and 7 days with ECT); this corresponds with delayed onset of response seen with conventional treatment; some authors suggest NMDA and glutamate systems constitute final common pathway associated with all treatments for depression.

Neuroplasticity: possible explanation for delayed therapeutic onset and glutamatergic effects of conventional treatments; functional brain imaging and postmortem studies of MDD show decreased brain volume in prefrontal cortex and hippocampus, disrupted functional connectivity, and reductions in glial cell numbers, pyramidal cell sizes, and synaptic density (particularly in dorsolateral prefrontal cortex and hippocampus); glutamatergic excitotoxicity — probably explains neurotrophic findings associated with depression; occurs when excessive levels of glutamate cause neurons to decrease expression of brain-derived neurotrophic factor (BDNF), critical in neuroplasticity, cell growth and differentiation, and early neural development; decreased BDNF results in dendritic retraction, reduced dendritic spine density and branching, and reduced synaptic strength.

Study (Larkin and Beartarouis, 2011): low dose of ketamine (0.5 mg/Kg, vs ≤4.5 mg/Kg commonly used for anesthesia) infused over 40 min yielded robust decreases in depression during first 72 hr after treatment; although some transient euphoria or psychosis produced, these could not account for antidepressive effects (which did not occur until 2-4 hr after infusion); results suggest rapid neuroadaptative changes occurring in brain and
glutamate systems that cause antidepressant response; response rate 50%; time to relapse 1 to 2 wk (average 7 days)

**Ketamine**: NMDA antagonist; structurally related to phencyclidine; widely used throughout world; particularly used in situations with limited monitoring, because of its safety profile (e.g., it stimulates rather than suppresses cardiopulmonary function); well tolerated from physiologic standpoint; wide margin of safety; low bioavailability when taken orally, which has led to failures in studies using oral doses for depression; in animals who have developed dendritic "shriveling" due to stress, ketamine stimulates growth of new neurons after 24 hr (reflected in functional improvements in excitatory postsynaptic potential); however, high doses do not produce this effect.

**Mechanism of action**: at postsynaptic NMDA and AMPA receptor sites, ketamine inhibits γ-aminobutyric acid (GABA)ergic inhibitory interneurons and thus causes upregulation of glutamate release into synaptic cleft; at lower doses, ketamine blockades NMDA receptors while leaving AMPA receptors unoccupied; this probably causes shunting of glutamate away from NMDA pathways and toward AMPA pathways, which negates NMDA receptors' inhibition of BDNF and upregulates AMPA's stimulation of BDNF

**Safety**: sympathomimetic (with transient effects on heart rate, blood pressure [BP], and cardiac output); contraindicated in patients with uncontrolled hypertension, elevated intracranial pressure, or glaucoma (due to association with elevated ocular pressure); emergence phenomena — at high doses, patients may experience hallucinations, delirium, or dissociation while emerging from anesthesia; these may be highly unpleasant and result in agitation; subanesthetic doses minimize these phenomena, but some psychotomimetic symptoms may still occur (speaker's study excludes patients who have personal history of or first-degree relative with psychosis); not found to induce mania in bipolar depression; common side effects — drowsiness; dizziness; lightheadedness; poor coordination (30% of patients); blurry vision; feeling strange or unreal (25%); headache, dry mouth, and slurred speech (20%); numbness or tingling (13%); study by Wan et al (2015) of 205 infusions of ketamine found that adverse effects typically disappeared after 2 to 4 hr in all patients

**Neurotoxicity**: observed in animal models, but at extremely high doses with questionable relevance to therapeutic use in depression; emergency department guidelines for use of ketamine in sedation do not regard long-term neurotoxicity as relevant issue

**Risk for addiction**: ketamine schedule III controlled substance; known to cause addiction in some patients; popular for recreational abuse (typically intranasal), but at doses much higher than those used to treat depression; complications in addicts — blader dysmotility; biliary dilatation; cognitive impairments; anxiety; flashbacks; social withdrawal; review article suggests cognitive impairment resolves with abstinence

**Long-term effects of low-dose ketamine**: relatively understudied; recent data suggest concerns over safety may be unfounded, with transient elevations in BP noted as only significant concern (monitoring required); psychiatric side effects — minimal increases in BPRS scores (from 4 to 4.2); mild levels of dissociation noted on Clinician-Administered Dissociative States Scale, but patients return to baseline within 4 hr; study (Wan et al, 2015) — participants did not crave or use ketamine or other substances outside research center; patients without predisposition to addiction do not develop addiction to ketamine after treatment

**Reducing risk for suicide**: ketamine uniquely effective; when compared to placebo, ketamine reduces risk for suicide and suicidal ideations in acute situation (measured via explicit questionnaires and implicit association tests)

**Suggested Reading**


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**Acknowledgments**

Dr. Marder spoke at the 20th Annual Psychopharmacology Update, held February 11-15, 2014, in Las Vegas, NV, and sponsored by the Nevada Psychiatric Association. To learn about the next Psychopharmacology Update, please visit npvspsychiatry.org. Dr. Paleos spoke at the NYU/Bellevue Psychopharmacology Annual Review, held March 7, 2015, in New York, NY, and sponsored by the NYU Post-Graduate Medical School. To learn about the next NYU/Bellevue Psychopharmacology Annual Review, please go to cme.med.nyu.edu/psychopharm. The Audio Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

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| Review Educational Objectives on page 1 | 5 minutes |
| Take pretest | 10 minutes |
| Listen to audio program | 60 minutes |
| Review written summary and suggested readings | 35 minutes |
| Take posttest | 10 minutes |
1. In a 2013 meta-analysis comparing 15 different antipsychotic (AP) medications, which of the following agents showed the strongest efficacy?
   (A) Olanzapine  (B) Risperidone  (C) Clozapine  (D) Haloperidol

2. In a population-wide study from Finland, conducted in 2009, which of these AP medications was associated with the highest rates of mortality?
   (A) Clozapine  (B) Chlorpromazine  (C) Risperidone  (D) Quetiapine

3. In which of these areas has newer AP medications shown superiority over older AP medications?
   (A) For positive symptoms of schizophrenia  (B) For negative symptoms of schizophrenia  (C) As maintenance therapy  (D) For suicidality

4. Which of these side effects are most strongly associated with older APs, when compared to newer APs?
   (A) Extrapyramidal symptoms (EPS) and prolactin elevation  (B) Hyperlipidemia and hypertension  (C) Insulin resistance and weight gain  (D) QT prolongation and sudden death

5. Which of these signs constitutes the best evidence a patient has developed the type of mild EPS commonly associated with newer AP medications?
   (A) Pacing and difficulty sitting  (B) Spontaneous movements and tremor  (C) Reduced arm swing when walking  (D) Cogwheeling

6. Which of these is the only AP agent known to actually lower prolactin levels rather than elevating them?
   (A) Asenapine  (B) Aripiprazole  (C) Paliperidone  (D) Ziprasidone

7. Which of these elements of the brain are responsible for the reuptake of glutamate and tend to show depletion in postmortem brain samples taken from individuals with depression?
   (A) Dendrites  (B) Glial cells  (C) Pyramidal neurons  (D) All the above

8. The atrophy seen in the brains of patients with depression is thought to occur as a downstream effect of glutamate toxicity, which reduces the expression of which of these chemicals?
   (A) \(N\)-methyl-D-aspartic acid  (B) Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid  (C) Brain-derived neurotrophic factor  (D) \(\gamma\)-aminobutyric acid

9. What dose of ketamine is most commonly used for the treatment of depression?
   (A) 4 mg/Kg  (B) 2 mg/Kg  (C) 1 mg/Kg  (D) 0.5 mg/Kg

10. Which of these side effects represents the biggest safety concern associated with low-dose ketamine?
    (A) Hypertension  (B) Glaucoma  (C) Bladder dysmotility  (D) Biliary dilatation

Answers to Audio Digest Psychiatry Volume 44, Issue 21: 1-B, 2-D, 3-C, 4-D, 5-D, 6-A, 7-A, 8-A, 9-D, 10-C

Attention, CME/CE Participants

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