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Editor-in-Chief

IV delivery of psychotropics could become a routine outpatient psychiatric procedure

A brave new era of IV psychopharmacotherapy

Starting an infusion might become part of your daily work

Most psychiatrists generally avoid starting an IV line on their patients these days, but delivering psychotropic medications by infusion has been employed in psychiatry for decades—mainly in cases of acute psychiatric emergencies.

IV pharmacotherapy might be evolving, however, to address the treatment of severe, chronic, intractable, and disabling disorders that have failed to respond to multiple oral formulations. In addition, IV therapy might be exploited to hasten onset of a therapeutic response.

In short, IV delivery of psychotropics might soon become a routine psychiatric “procedure.”

In the past

Apart from the desperate measures of pentylenetetrazol-induced seizures for depression and insulin coma for schizophrenia—both eventually discarded—psychiatrists have used IV pharmacotherapeutic interventions since the dawn of psychopharmacology in the 1950s. These include:

- **Anticholinergics** (benztropine, diphenhydramine) to rapidly relieve acute and distressing dystonic reactions, such as oculogyric crisis
- **Droperidol** (the highly sedating cousin of haloperidol) for severe agitation or aggressive behavior in an emergency setting

- **Haloperidol** for delirium in the intensive care unit

- **Benzodiazepines** for severe anxiety and panic attacks (although the IM route is preferable)

- **Clomipramine** to potentiate the effect of a selective serotonin reuptake inhibitor in treatment-resistant depression

- **Valproate** to accelerate mood stabilization in acute mania.

The present

Recently, a mini-avalanche of novel studies has signaled a paradigm shift to IV therapy for refractory unipolar and bipolar depression.

Ketamine. Administering the *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine (a cousin of phencyclidine and a well-known drug of abuse with psychotogenic properties) by IV infusion (0.5 mg/kg) produces rapid improvement, sometimes complete remission, of chronic, treatment-resistant depression. The effect seen in 1 or 2 hours matches what oral antidepressants accomplish in 6 to 8 weeks in a responsive patient.^{1,2} The response to IV ketamine lasts approximately 1 week and is initially associated with transient dissociation.

Another reported benefit of IV ketamine is rapid reversal of suicidal intent.³ This effect is envisioned as a future alternative to hospitalizing patients brought to the emergency room after a suicide attempt.

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To be clear: The long-term (maintenance) safety and efficacy of repeated infusions of IV ketamine to maintain response in chronic, treatment-resistant depression has *not* been studied.

IV ketamine therapy for severe depression is a dual paradigm shift: 1) it uses the IV route and 2) it modulates the glutamate ion-channel receptor NMDA—a major departure from the 50-year-old monoamine hypothesis of depression, in which a deficit of serotonin and/or norepinephrine was proposed. The mechanism of action of IV ketamine appears to be instant triggering of neuroplasticity in the mammalian target of rapamycin (mTOR), as observed in animal studies. A significant surge in brain-derived neurotrophic factor appears to be involved as well.

Scopolamine. Another novel IV treatment for depression was reported recently,⁴ based on old studies in which tearfulness and dysphoria were induced by increasing cholinergic activity with IV physostigmine. The anticholinergic drug scopolamine was administered to depressed patients by pulsed IV infusion (4.0 µg/kg over 15 minutes), and rapid improvement in depression was observed within 72 hours in patients with unipolar and bipolar depression. Anticholinergic side effects were mild; women responded better than men.

Nitroprusside. A similar breakthrough with IV pharmacotherapy was recently reported in schizophrenia, in which traditional oral antipsychotic treatment is limited to suppressing positive symptoms, leaving negative symptoms and cognitive deficits unchanged. The old

Another reported benefit of IV ketamine is rapid reversal of suicidal intent

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Benztropine • Cogentin	Pentylentetrazol •
Clomipramine • Anafranil	Metrazol
Diphenhydramine •	Physostigmine •
Benadryl	Antilirium
Droperidol • Inapsine	Scopolamine • Scopace,
Haloperidol • Haldol	Transderm-Scop
Ketamine • Ketalar	Valproate • Depacon
Nitroprusside •	
Nitropress	

antihypertensive drug nitroprusside, which modulates nitrous oxide and, by extension, NMDA, was administered IV to a small sample of patients with schizophrenia.⁵ Significant improvement was observed not only in positive (psychotic) symptoms, but also in negative and cognitive symptoms. Improvement occurred within a few hours and lasted for as long as 4 weeks. Studies are underway to replicate the investigators' findings about this potentially ground-breaking and novel approach to schizophrenia.

For the future

Given these recent successes, it is reasonable to speculate that IV drugs might someday become a major tool in the practice of psychiatry—transcending emergent uses (suicidal, homicidal, and delirious states) and becoming a mainstream treatment for acute episodes of psychosis, mania, depression, and anxiety. In addition, research might reveal that medications already approved for oral delivery exert a more robust response and a more rapid onset of action when delivered IV—assuming no serious safety issues arise.

Advances in our understanding of the neurobiologic basis and pathophysiology of psychiatric disorders might provide clues to agents that are not even on the current radar screen of psychiatry's pharmacopoeia. Treatment-resistant conditions are obvious initial candidates for IV pharmacotherapy, but so might be acute episodes of psychosis, mania, and depression, and panic attacks. Just as status epilepticus requires IV, rather than oral, delivery of an anticonvulsant, we might conceptualize acute psychotic, mood, and anxiety episodes as emergent conditions of *status psychiatricus* that require rapid stabilization with IV medication instead of a pill.

The bottom line?

IV delivery of drugs might soon be a routine psychiatric "procedure." Better brush up on your skills for starting an infusion!

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