KETAMINE, DEPRESSION, AND ECT

- Theory and practice

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CONFLICTS

- Financial conflicts: Nil
- Academic conflicts:
  - I have 6-7 years of experience with ketamine in depression
  - I support a view that ketamine, especially oral ketamine, can be a very useful and even crisis-intervention treatment in special contexts

ISSUES

- Ketamine for depression
  - Is ketamine the new ECT?
- Ketamine anesthesia in ECT for depression
  - Does it improve ECT outcomes?
- Learning objective
  - ECT practitioners should understand what they are up against.

COMMENT

- Ketamine has the potential to change the way we manage depression.

- Knowing how to use ketamine may sometime become a need in psychiatric training, much as training in the administration of ECT is a need (Rao and Andrade, IJP 2017).

KETAMINE FOR DEPRESSION: OUTLINE

- General introduction
- Efficacy
- Adverse effects
- Indications vs contexts
- Dose, duration of administration, route of administration, frequency of administration, maintenance therapy
- Ketamine vs ECT

LOOKING BACK

- Iproniazid and imipramine, entered in the 1950s.
- In later years:
  - TCA, MAOIs, SSRIs, SNRIs, NARIs, NaSSAs, etc.
- These drugs differ in mechanisms, action on specific symptoms, AEs, metabolism, PK, drug interactions etc.
- Efficacy profile and time to response, however, are broadly similar.
  - But dual acting drugs may be > SSRIs for efficacy.

NEEDED: A CLOZAPINE FOR DEPRESSION

- Ketamine is novel among the available antidepressants
  - In mechanism, in onset of action, in magnitude of effects
- Ketamine is not a clozapine for depression.
  - But it may be interposed between AD drugs and ECT
  - Or may have use in special contexts

KETAMINE (Andrade, JCP 2017a)

- Introduced as an anesthetic drug around 1970
- Dosing in anesthesia: 2-3 mg/kg for induction
- Has demonstrated efficacy
  - In adult and pediatric practice
  - In subanesthetic doses
  - For many off-label indications
- Ketamine is NOT an anesthetic drug
  - What a drug is depends on indication and manner of administration
  - Consider aspirin, quetiapine, lamotrigine etc.

IN LIGHTER VEIN

- Ketamine is an antidepressant drug.
- Some medical professionals use it in high doses for anesthesia.

KETAMINE: OFF-LABEL INDICATIONS

- Pain management
  - Emergency room, post-operative, cancer pain, refractory headache
  - 'Buddy drug' on the battlefield
- Agitation, violence
  - Pre-emergency and emergency room
- Pediatric sedation in dentistry, radiology
- Depression
- ? GAD, SAD, OCD, PTSD

INITIAL STUDIES: 1

- Krystal et al (AGP 1994):
- 19 normal volunteers
- 0.1, 0.5 mg/kg iv across 40 min
- Study of psychotomimetic and other effects
- Set the default parameters for future study

INITIAL STUDIES: 2 (Berman et al, BP 2000)

- Crossover RCT in MDD (n=7)
- 0.5 mg/kg iv across 40 min in MDD
- Antidepressant effect evident at 4 h
- Persisted at 3 days

INITIAL STUDIES: 3 (Zarate et al, AGP 2006)

- Drug-resistant MDD (n=18)
- 0.5 mg/kg iv across 40 min
- Crossover RCT
- At 1 day, response rate 71%, remission rate 29%
- Response attenuated but still evident at 1 wk
- Not everybody responds, remits

Ketamine for depression: Meta-analysis (Kishimoto et al, Psychol Med 2016)

- 9 RCTs; pooled N=234
- Ketamine > control
- Antidepressant benefit evident at 40 min
- Peaked at 1 day
- Lost in 10-12 days
- Almost all of the data from MDD patients
- A few studies included bipolar patients
  - Benefits lost earlier, as in 3-5 days

SUICIDAL PATIENTS: 1

- Case reports, open studies, RCTs, meta-analysis
- Single and repeated dosing with iv ketamine
- Attenuation of measures of suicidality in TRD
- Benefits tend to wear off within a week
- Antisuicidal effect is partly independent of the AD effect
- (Price et al BP 2013 & Depr Anx 2014; Murrough et al Psychol Med 2015; Burger et al, Mil Med 2016; Wilkinson et al, Am J Psychiatry 2017; Andrade, J Clin Psychiatry 2018)

SUICIDAL PATIENTS: 2

- Domiciliary treatment has also been given in 2 patients
  - Grande, PCC CNS Disord 2017

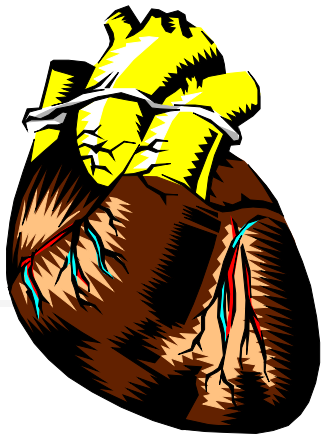
ADVERSE EFFECTS: 1

- Meta-analysis of 9 RCTs (N=234)
- All cause discontinuation: no difference between ketamine and controls
- Dissociative and psychotomimetic effects more common with ketamine
  - But shortlasting (usually, 2 h max)
  - Usually, not clinically significant
- Kishimoto et al (Psychol Med 2016)

ADVERSE EFFECTS: 2 (Wan et al, JCP 2015)

- Pooled data from 3 MDD RCTs
  - N=97; 205 ketamine sessions
- Only 4 sessions discontinued because of AEs
- Commonest AEs in the initial 4 h
  - Drowsiness, dizziness, poor coordination, blurred vision, feelings of strangeness or unreality
- AEs wear off over the subsequent hours

ADVERSE EFFECTS: 2 (Wan et al, JCP 2015)



- Transient mean peak increases:
  - 20 mm Hg for SBP
  - 13 mm Hg for DBP
- Nearly 30% of patients had transient increases:
  - SBP>180 mm Hg
  - DBP>110 mm Hg
  - HR>110 bpm
- Is this a concern? Consider ECT, exercise
  - Almost all patients will be 'fit' for ketamine

ADVERSE EFFECTS: 4

- AEs risk and severity are both dose-dependent
  - Lai et al, WJPB 2014; Loo et al, Acta Psychiatrica Scand 2016
- AEs, in general, peak during the session and wane in 2 h max
  - Rarely, longer lasting AEs, if any wane in 4-24 h
  - Andrade, JCP 2017a

ADVERSE EFFECTS: 5

- During ketamine iv sessions, blood levels are well below those associated with ketamine anesthesia
  - And below levels associated with awaking from anesthesia
- Patients are almost always awake all through the ketamine session
- O2 saturation is normal
- Respiration is normal
- (Wan et al, JCP 2015; Sanacora et al, JAMA Psychiatry 2017)

ADVERSE EFFECTS: 6

- 6 case reports of manic switch
  - Reviewed by Allen et al, Bipolar Disord 2019
- Mania in bipolar depression may be preventable by including antipsychotic or mood stabilizer co-medication
  - Rybakowski et al, Int J Psychiatry Clin Pract 2017

ADVERSE EFFECTS: 7

- Long-term, high dose abuse has been associated with medical risks such as cystitis.
- No long-term consequences have been identified with low dose, intermittent, controlled medical use.
  - Andrade, JCP 2017a
- Ketamine rated as a generally very acceptable treatment.
- AEs may decrease during maintenance therapy.

INDICATIONS vs CONTEXTS: 1

- Indications for ECT are depression, mania, schizophrenia
- Clinical contexts for ECT are severe illness, suicide risk, antidepressant drug refractoriness, presence of catatonic or psychotic symptoms, etc.
- Administrative and social contexts for ECT are need for rapid recovery to return the patient home earlier, to clear hospital beds earlier, etc.
- Devanathan and Andrade, 2011

INDICATIONS vs CONTEXTS: 2 (Andrade, JCP 2017b)

- Indication for ketamine is MDD
  - Possibly bipolar depression, as well
- Contexts for ketamine are
  - Severe illness
  - Suicide risk
  - Social need for rapid response
  - Treatment refractoriness
  - Acceleration/improvement of response to ADs/ECT

INDICATIONS

- Most studies recruited patients with MDD
- A few studies included patients with bipolar depression
- It is possible that benefits are lost earlier in patients with bipolar depression (3-5 vs 7-10 days).

CONTEXTS: SEVERE, REFRACTORY ILLNESS

- Almost all studies recruited patients with severe illness
- Almost all studies recruited patients who were medication-refractory
- There may not be justification for use in non-severe, non-refractory patients
  - Unless other contexts are present

CONTEXT: SUICIDE RISK: 1

- Especially when the patient cannot be admitted or otherwise supervised
- Contributes to crisis intervention
  - Zigman and Blier, J Clin Psychopharmacol 2013
- Helps until other interventions are instituted and take effect.
- Data from open studies, RCTs, meta-analysis
  - Andrade, JCP 2017b; 2018; Rao and Andrade, IJP 2017

CONTEXT: SUICIDE RISK: 2

- Effect size is large (meta-analyses)
  - Bartoli et al, Neurosci Biobehav Rev 2017; Wilkinson et al, Am J Psychiatry 2017)
- Benefits evident in a day
  - Price et al, BP 2009, Price et al, Depress Anx 2014; Murrough et al, Psychol Med 2015
- In emergency settings, benefits evident even in 40 min
  - Larkin et al, Int J Neuropsychopharmacol 2011; Burger et al, Mil Med 2016

CONTEXT: SUICIDE RISK: 3

- Benefits wear off in 7-10 days
  - Larkin et al, Int J Neuropsychopharmacol 2011; Murrough et al, Psychol Med 2015; Wilkinson et al, AJP 2017
- But time thus gained allows for the initiation of other interventions.
- Ketamine may become an important tool to manage suicidal depression in clinical practice
  - Rao and Andrade, IJP 2017

CONTEXT: LIFE CIRCUMSTANCES

- ECT has been used for urgent social indications such as weddings and examinations
  - Kellner et al, J ECT 2009; Devanathan and Andrade, 2011
- Ketamine can be used for similar situations
  - Fast onset, greater benefits than ECT
  - Less cognitive risks than ECT
- Dosing may need to be repeated if the social context persists when the benefit wears off

CONTEXT: AUGMENTATION OF ROUTINE AD TREATMENT (Hu et al, Psychol Med 2016)

- 4-week RCT
- Escitalopram (10 mg/d) + Ketamine (iv) vs saline
- 27 patients with severe, nonpsychotic MDD
  - Response rates, 92% vs 57%
  - Remission rates, 77% vs 14%
  - Time to response, 6.4 vs 26.5 days
  - Time to remission, 14 vs 27 days
- All cause discontinuation, 20% vs 7%
- No drop out due to AEs

CONTEXT: AUGMENTATION OF ROUTINE AD TREATMENT (Hu et al, Psychol Med 2016)

- 56% of the sample was medication refractory
- Ketamine > saline in whole sample as well as in refractory subsample
- No analysis of nonrefractory sample presented
- Therefore cannot generalize results to MDD population in general

CONTEXT: USE WITH ECT: 1

- As part or whole of ECT anesthesia
- Two meta-analyses:
- McGirr et al (BJP 2017)
  - 10 RCTs, N=602
- Li et al (Eur Neuropsychopharmacol 2017)
  - 16 RCTs, N=675

CONTEXT: USE WITH ECT: 2

- McGirr et al: No advantage for ketamine at the end of the ECT course
- Li et al: Ketamine use associated with acceleration of early response at 1-2 and at 3-4 weeks
- Both meta-analyses: Increase AE risk, especially postictal agitation/confusion
- It may be hard to improve outcomes with ECT, which is a gold standard treatment (Andrade, BJP 2018)

CONTEXT: USE WITH ECT: 3 Zheng et al (JAD 2019)

- 17 RCTs, pooled N=1035 MDD patients
- Ketamine alone/with other anesthesia drugs (N=557)
- Comparator: Other anesthesia drugs alone (N=478)
- Ketamine + other > other for early outcomes
- Ketamine + other not superior at post-ECT, end of study assessments
- Ketamine alone not superior at any time point

CONTEXT: USE WITH ECT: 4

- Implications:
  - We treat patients with ECT to elicit remission
  - Patients may show faster initial recovery with ketamine in anesthesia
  - At the ECT endpoint, there is no difference (ceiling effect; gold standard cannot be improved upon)
  - Use of ketamine in anesthesia increases adverse post-anesthesia recovery outcomes
  - Data do not support a role for ketamine in ECT anesthesia

CONTEXT: PSYCHOTIC SYMPTOMS

- Psychotic symptoms may NOT be a contraindication.
- At least 2 case reports demonstrate efficacy in psychotic depression.
- Psychotic worsening may be prevented using concurrent antipsychotic medication (Ribeiro et al, BP 2016)
- Nevertheless, use with caution, if at all
- Andrade, JCP 2017b

Chittaranjan
Andrade

TREATMENT CONSIDERATIONS: 1. ROUTE OF ADMINISTRATION

- Oral (flavored), sublingual (lozenges), transmucosal
- Intranasal
  - Esketamine has US FDA approval (March 2019)
- Intravenous, intramuscular, subcutaneous
  - IV is the best studied
  - IV has the most impressive rituals
- Rectal

TREATMENT CONSIDERATIONS: 2. DOSE

- Benefits are probably dose-dependent
  - For i.v., between 0.3 and 0.8 mg/kg i.v.
- Dose depends on route of administration
- Dose-titration to efficacy may be required

TREATMENT CONSIDERATIONS: 3. RATE OF ADMINISTRATION

- Can be given as a bolus (oral, sc, im)
- Across up to 5 min (in)
- Across 2-100 min (iv)

TREATMENT CONSIDERATIONS: 4. NUMBER OF ATTEMPTS

- Declare futility if no benefits in 3 (max, 6) sessions

TREATMENT CONSIDERATIONS: 6. DURATION OF CONTINUATION

- Treatments work only for as long as they are taken
- Maintenance trt has been described by IN, sc, im, and iv routes in case reports, controlled trials, and uncontrolled trials at 2-7 day intervals for 1 mo to up to 5 years
- Session spacing individualized to need

TREATMENT CONSIDERATIONS: 7. CONCURRENT MEDICATIONS

- Some studies, especially the initial ones, studied ketamine monotherapy
- Many subsequent studies used ketamine in addition to ongoing treatments
- As with ECT, it may be best to continue ongoing ADs during ketamine treatment
- After all, AD maintenance therapy will be required post-ketamine.
- (Andrade, JCP 2017a,e)

INTRANASAL ESKETAMINE

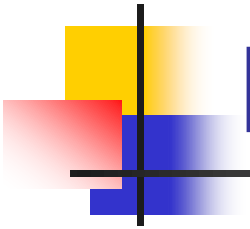
- Approved as an antidepressant augmentation agent for TRD
- Fixed dosing; 56 or 84 mg.
- Weeks 1-4, dose twice weekly
- Weeks 5-8, dose once weekly
- Weeks 9 onwards, dose once or twice a week
- Treatment under a special REMS system
- 2 h monitoring mandated

MECHANISM OF ACTION

- Does ketamine work as an opioid?
  - Naltrexone dramatically blocked the antidepressant but not the dissociative effects of ketamine at Days 1 and 3 post infusion in TRD.
  - Williams et al, Am J Psychiatry 2018
- Ketamine may merely be a symptomatic treatment
  - Not a curative treatment
  - As with paracetamol that treats pain or fever, but not the cause

GENERAL NOTE ON SAFETY

- Ketamine is a very safe drug
  - Much safer than other anesthetics
  - Does not depress cardiovascular or respiratory responses
- Has even been safely administered by nurses (with no experience in sedation) in emergency care (Bisanzo et al, Ann Emerg Med 2012)
- Ketamine is no more heroic or risky than ECT, clozapine, or a large number of other drugs in the pharmacopeia (Andrade, JCP 2017d)



KETAMINE vs ECT: 1

- There are no head to head studies published as yet, though some are ongoing/planned.

KETAMINE vs ECT: 2

- The two treatments seem indicated in largely non-overlapping contexts
- Ketamine
  - Suicidal patients
  - Patients who need to continue to work
  - Treatment-refractory patients
- ECT
  - Severely depressed, suicidal, psychotic, and/or catatonic patients
  - Treatment-refractory patients

KETAMINE vs ECT: 3

- The effects of ketamine wear off rapidly
  - Maintenance treatments need to be given at short intervals
  - All sessions are not equal in efficacy
  - Patients rarely remit and stay in remission
  - Does not seem a viable long-term solution
- The effects of ECT are more persistent
  - Maintenance treatments, if required, can be spaced out more widely
  - Treatment effects are more robust

Ketamine for Depression, 1:
Clinical Summary of Issues Related to Efficacy, Adverse Effects, and Mechanism of Action

Chittaranjan Andrade, MD

Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

Ketamine is an anesthetic drug that is also used for off-label indications such as the mediation of analgesia and sedation in various settings. It is additionally recognized as an agent with

Introduction

Antidepressant drugs, starting with iproniazid an psychiatry in the 1950s.[1] These and dozens of othe were marketed (and many withdrawn) in the deca drugs included tricyclic antidepressants, monoami selective serotonin reuptake inhibitors, serotonin reuptake inhibitors, norepinephrine reuptake inhib some antidepressant classes including a large numb represented by a single drug.

Antidepressant drugs: different, yet the same. T antidepressants vary across and within classes c mechanism of action, efficacy against specific sym profile, metabolic pathways, and drug interactions, is, however, little difference in antidepressant efficac the possible exception that drugs with dual serotoni mechanisms may be marginally more effective than reuptake inhibitors.[2]

Needed: a "clozapine for depression." Clin

Clinical and Practical Psychopharmacology

Ketamine for Depression, 2: Diagnostic and Contextual Indications

Chittaranjan Andrade, MD

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ABSTRACT

There is a substantial body of literature comprising anecdotal material and descriptions of uncontrolled and randomized controlled trials addressing the use of subanesthetic doses of ketamine for the off-label treatment of major depressive episodes. This article examines diagnostic indications for the off-label use of ketamine as an antidepressant and possible contexts in which ketamine may be trialled. Ketamine is indicated in patients who are

Introduction

A previous article in this column[1] summarized is the efficacy, adverse effects, and possible mechanism(subanesthetic dosing with ketamine in the treatment The present article examines possible diagnostic indicati contexts for the use of ketamine as an off-label antide 1). Readers may note here that the distinction betw indications and clinical contexts was made previously electroconvulsive therapy (ECT). In explanation, depress schizophrenia are examples of indications for ECT, and medication-refractory illness, presence of catatonic symp of psychotic symptoms, presence of suicidality, and the ne the patient early are examples of clinical and administra which the use of ECT may be preferred.[2]

Diagnostic Indications

The antidepressant efficacy of subanesthetic doses o been specifically studied in patients who were in a m episode. Antidepressant benefits were observed to achiev clinical significance within 1–4 hours of ketamine admi benefits peak after a day and are progressively lost 3–12

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Ketamine for Depression, 3:
Does Chirality Matter?

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ABSTRACT

Ketamine is a racemic mixture of the enantiomers *R*-ketamine and *S*-ketamine (esketamine). *S*-ketamine has greater analgesic and anesthetic effects than *R*-ketamine and is less likely to cause psychotomimetic and other adverse effects. There is therefore an emerging interest favoring the use of *S*-ketamine over racemic ketamine when the drug is used for analgesia or anesthesia. This article

Previous articles in this column summarized issue efficacy, adverse effects, and possible mechanism ketamine in the treatment of depression[1] and sugges and contexts for the use of ketamine as an off-label a The present article examines whether chirality is antidepressant action of subanesthetic doses of ketami

Terminology

Isomers are chemical substances with the same chem a different chemical structure, that is, a different arra atoms in the molecule. This difference usually results in exhibiting different properties. There are 2 important t structural isomers and stereoisomers.

Structural isomers are chemical substances tha positions at which atoms or functional groups are co molecule. As an example, the difference may lie in the p a halogen atom or a hydroxyl group is attached to a hyd or a benzene ring. Thus, 1-fluoropropane and 2-flu structural isomers that differ in the position (indicated at which the fluorine atom substitutes for hydrogen molecule.

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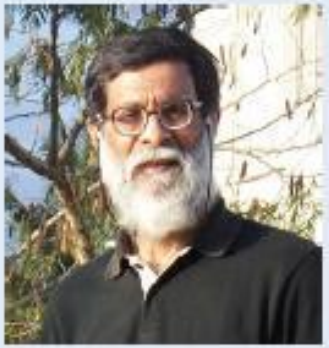
Ketamine for Depression, 4:
In What Dose, at What Rate, by What Route, for How Long, and at What Frequency?

Chittaranjan Andrade, MD



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ABSTRACT

Background: Ketamine, administered in subanesthetic doses, is an effective off-label treatment for severe and even treatment-refractory depression; however, despite dozens of studies across nearly 2 decades of research, there is no definitive guidance on matters related to core practice issues.

Introduction

Previous articles in this column summarized iss to the efficacy, adverse effects, and possible me of action of ketamine in the treatment of d suggested indications and contexts for the use o as an off-label antidepressant[2]; and examined iss to the choice of ketamine enantiomer vs the use ketamine.[3] The present article examines issues dosing, rate of administration, route of admi duration of treatment, and frequency of sess ketamine is used in subanesthetic doses for the of depression, especially treatment-resistant dep

What Dose?

Ketamine was administered by the intravenous in the doses of 0.1 and 0.5 mg/kg when its psycho and other effects were formally studied.[4] T randomized controlled trials (RCTs) of sub

Clinical and Practical Psychopharmacology

Ketamine for Depression, 5:
Potential Pharmacokinetic and Pharmacodynamic Drug Interactions

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ABSTRACT

Ketamine, administered in subanesthetic doses, is gaining recognition as an off-label treatment for severe and even treatment-refractory depression. This article explores potential pharmacokinetic and pharmacodynamic drug interactions of relevance to the use of ketamine in depression. Sparse evidence suggests that ketamine will not induce clinically significant drug interactions except to

Introduction

Previous articles in this column considered issues rel the efficacy, adverse effects, and possible mechanism(s) o of ketamine in the treatment of depression[1]; discussed ind and contexts for the use of ketamine as an off-label antidep evaluated the antidepressant benefits and risks of *R*-ke *S*-ketamine, and racemic ketamine[3]; and reviewed issues re dosing, rate of administration, route of administration, d of treatment, and frequency of sessions when ketamine is subanesthetic doses to treat depression.[4] The present article e potential pharmacokinetic and pharmacodynamic interactio ketamine is used as an off-label treatment for depression.

The Effect of Ketamine on Cytochrome P450 (and Other) Metabolic Enzymes and Their Substrates

In vivo studies in a rodent model found that a single ketamine had no effect on cytochrome P450 (CYP)1A, CYI and 2E1 enzymatic activity; however, there was mild (13 possibly clinically nonsignificant inhibition of the activity of C and mild to modest (18%–32%) inhibition of CYP3A.[5,6] Ke induced reduction in CYP3A4 activity may involve an inhib

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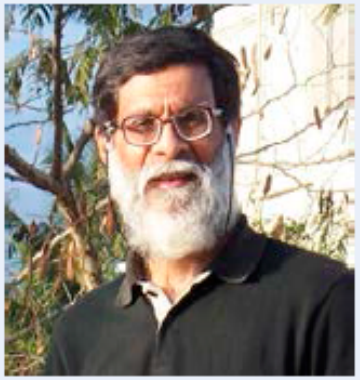
Ketamine for Depression, 6: Effects on Suicidal Ideation and Possible Use as Crisis Intervention in Patients at Suicide Risk

Chittaranjan Andrade, MD



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ABSTRACT

Previous articles in this column discuss effects, and possible mechanism(s) of doses of ketamine in the treatment of dep and contexts for the use of ketamine as an the antidepressant benefits and adverse eff enantiomers[3]; issues related to dosing, rate o administration, duration of treatment, and fr ketamine is used to treat depression[4]; and pote pharmacodynamic interactions when ketami treatment for depression.[5] The present artic ketamine on suicidal ideation and its possibl crisis intervention in patients at suicide risk.

The first randomized, double-blind, place trial of subanesthetic dosing with ketamin

Clinical and Practical **Psychopharmacology**

Oral Ketamine for Depression, 1:

Pharmacologic Considerations and Clinical Evidence

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ABSTRACT

Ketamine has gained visibility as a unique, powerful, rapid-acting, off-label treatment for depression. Earlier articles in this series summarized issues related to the efficacy, adverse effects, and mechanisms of action of ketamine as an off-label treatment for depression[1]; diagnostic and contextual indications for ketamine[2]; benefits and risks of *R*-ketamine vs esketamine vs racemic ketamine[3]; treatment considerations, such as dosing, route of administration of the drug, rate of administration of the drug during a session, frequency of treatment sessions, and duration of ketamine therapy[4]; pharmacokinetic and pharmacodynamic interactions between ketamine and other treatments[5]; and the use of ketamine as an emergency intervention in patients at risk of suicide.[6]

Clinical and Practical Psychopharmacology

Oral Ketamine for Depression, 2:
Practical Considerations

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ABSTRACT

The oral route of administration is probably the least expensive and most convenient way to administer ketamine in indicated contexts in depressed patients. Because only 20%–25% of orally administered ketamine reaches systemic circulation, oral doses of about 2.0–2.5 mg/kg may need to be administered to achieve equivalence to intravenously administered ketamine. In case reports, case series, standard operating practice in

Ketamine, originally approved as an anesthetic drug, is gaining ground as an intervention for patients with treatment-resistant depression (TRD), depression with serious suicidal ideation, and perhaps depression in certain other contexts, as well.[1,2] In March 2019, the US Food and Drug Administration (FDA) approved the use of intranasal esketamine, in conjunction with an oral antidepressant, for patients with TRD. The treatment will be made available only through a restricted distribution system in a Risk Evaluation and Mitigation Strategy program and will need to be administered in a certified medical office where the patient can be monitored for at least 2 hours after dosing.[3]

On the one hand, the FDA approval will make (es)ketamine formally available to patients with TRD; the approval will thus add to the treatment options described for patients with this difficult-to-treat condition. On the other hand, because of the restrictions under which the intervention will be marketed, accessibility could be poor. Affordability is also likely to be a problem. Finally, intranasal (es)ketamine is unlikely to become available, accessible, and/or affordable in other parts of the world in the near future. It is therefore necessary to consider

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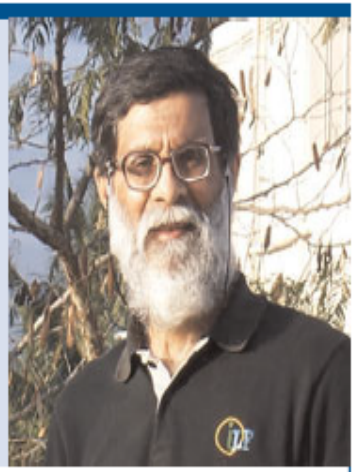
Editorial

Ketamine as anaesthesia for ECT: is there room to improve a gold standard treatment?

Chittaranjan Andrade



Summary

One meta-analysis of ketamine anaesthesia for electroconvulsive therapy found no improvement of end-point antidepressant outcomes; another meta-analysis with a broader range of included trials found that ketamine improved both early and late outcomes. If ketamine anaesthesia is useful, researchers may need to look for benefits earlier during the treatment course.

Declaration of interest

None.

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EDITORIAL

Choosing the Primary Outcome in Electroconvulsive Therapy Trials and the Art of Asking When, Besides What

AQ1 *Chittaranjan Andrade, MD*

Ketamine has been used in electroconvulsive therapy (ECT) anesthesia in 2 ways: in full anesthetic dose as the sole anesthetic agent or in subanesthetic dose to augment another anesthetic drug. When administered outside the context of ECT, subanesthetic dosing with ketamine has dramatic antidepressant action.[1] So might the use of ketamine in ECT anesthesia, either in subanesthetic dose or in full anesthetic dose, enhance the antidepressant effect of ECT? This question has been examined in randomized controlled trials (RCTs), and the RCTs have been summarized in several meta-analyses.

In one meta-analysis, the use of ketamine for anesthesia was found to be of no advantage in ECT-treated depressed patients when outcomes were assessed at the end of the ECT course. This finding held

Ketamine and Electroconvulsive Therapy for Depression

Chittaranjan Andrade, MD

Ketamine anesthesia was introduced about half a century ago. In recent decades, this drug, in subanesthetic doses, has also demonstrated efficacy for off-label indications including treating acute and chronic pain, treating agitation, treating depression, and inducing sedation. Thus, there are studies of subanesthetic dosing with ketamine for treating pain in emergency medicine settings, treating postsurgical pain, treating medication-refractory headache, reducing agitation and violence in prehospital and emergency settings, and sedating children in dental and radiological settings.[1]

The last decade has also seen a spurt of research on subanesthetic dosing with ketamine in patients with depression.[1] Before the advent of ketamine, the treatment of depression was based on variations on a theme of neuromodulation of serotonin, norepinephrine, and dopamine using drugs that had a wide range of actions on these neurotransmitter systems. Ketamine does not increase or decrease the reuptake of these neurotransmitters, does not affect their synthesis or metabolism, and does not act on the receptors on which they act. Although the antidepressant mechanism of ketamine remains unresolved, it appears that ketamine is not the only drug with psychotomimetic properties that has efficacy against depression and other psychiatric disorders; psilocybin, ayahuasca, methylenedioxymethamphetamine, and lysergic

ENFIN…

- That's it, folks; thanks for listening!