Rapid Treatments for Psychiatric Disorders

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Disclosures

Cristina Cusin 2011-2016:

– Speaking/CME/Consulting: Janssen, AZ
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  Acyliccucurbit[N]uril type molecular containers to treat intoxication and substance abuse
Definition of **rapid**?

- What does it mean “rapid”?
- “Rapid” compared to what?
- How do we compare with other specialties? (cardiology, anesthesia, neurology - stroke, pain, infectious disease)
- If you had acute pain from kidney stone and the only ‘effective’ treatment was a drug with a chance of improvement of 45% in 6 weeks how would you feel?
Rapid treatment of acute psychosis

- 24 patients with acute functional psychoses (schizophrenia or mania) were treated with IM haloperidol in a three-hour period.
- 5mg -> +10 mg Q30min vs 5mg-> +5mgQhr
- There was almost complete remission of cardinal symptoms (thought disorder, hallucinations, and delusional activity) in this period for 11 patients. Acute dystonia, easily reversed, was the only significant side effect

Anderson WH, American Journal Psychiatry, 1976, 133 (9) 1076-1078
Rapid for what problem?
(Hint: Think emergency room setting)

• Violent behavior
• Psychosis
• Intoxication/Overdose
• Withdrawal
• Drug reaction or interaction
• Anxiety/Panic
• Depression /Suicidality
Rapid for what problem? - II

- Route of administration of drugs (IV/IM)
- Contain/restrain/stabilize
- Administer something that solve the problem (i.e. naloxone for opiate OD) or stabilize (IV benzodiazepine for alcohol withdrawal)
- We have “treatments” for conditions with known etiology
- Do we have treatments for conditions of unknown etiology?
How do we treat acute psychiatric problems?

- Etiology not known
- Acute onset or worsening
- Old (cheap) drugs vs new expensive drugs ($$)
- What treatment is more efficacious?
- Do we have guidelines?
Sometimes is harder than you think

- **Hypothermia**: Etiology known ("fell in the Charles river in January" - college bet gone wrong)
- Acute onset - **clearly known**
- Cheap available treatment - **heat**
- Do you really want a RAPID tx for hypothermia? – rapid is LETHAL
- ED doctor must combine rapid **AND thoughtful**
Rapid “treatment” of agitation?

- Still need to rule out organic causes of delirium/agitation/psychotic symptoms (check lytes, CBT, toxins, PE, stroke, etc)
- What is the best pharmacologic treatment for non-organic psychosis?
- comparative effectiveness are very hard to conduct
Historical prospective

- psychiatric hospitals have always needed to sedate patients.
- ‘ Episodes of violence should be treated with explanation, suggestion, analysis or, where necessary, by hydrotherapy or drugs’ (Henderson and Gillespie, 1927) (notice drugs are LAST)
- initial chemical agents employed were opiates, hyoscine (IM) and digitalis; chloral was synthesized in 1869 and replaced opiates
- paraldehyde, barbiturates, bromides and anticholinergic agents 1850-1950s
- Insulin coma and ECT proposed as “disease specific”
Historical prospective

• 1955 1st advertisement for a drug in the Journal of Mental Science. Reserpine ‘induces a state of mental quietitude and relaxation’
• 1957 advertisements for the phenothiazine drugs Pacatal (mepazine) and Sparine (promazine hydrochloride)
• The first advertisement as antipsychotic was Stelazine (trifluoperazine) in 1959, with a claim that the drug is ‘specific for the hallucinated, delusional and aggressive psychotic’
• By 1962 there were a number of pharmaceutical advertisements, constituting 65% of the total of advertisements, compared with 17% in 1952
• ‘drug-induced rigidity’, or the ‘Parkinsonoid state’, produced by antipsychotics ‘may not be deleterious’ in emergency situations and that antipsychotics ‘offer an excellent alternative to the physical measures that might otherwise be required in acute situations’ (1972)
Guidelines?

- ‘The experts’ recommendations for medication to treat agitation that appears to be due to a primary psychiatric disturbance depends on the provisional diagnosis (Allen et al., 2001)
- the practice of ‘rapid tranquillisation is not underpinned by a strong evidence base’ (Taylor et al., 2012), although few large trials have been conducted
Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine.

- 301 aggressive patients randomized to receive IM midazolam (15 mg) or IM haloperidol (10 mg) + promethazine (50 mg).
- (89%) of patients given midazolam were tranquil or asleep after 20 minutes compared with 67% of those given haloperidol plus promethazine.
- By 40 minutes, midazolam still had a statistically and clinically significant 13% relative advantage.
- After 1 hour, about 90% of both groups were tranquil or asleep.

TREC collaborative group BMJ 2003 Sep 27; 327(7417): 708–713.
Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting. Pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine.

- 200 patients randomized to receive IM lorazepam (4 mg) or IM haloperidol (10 mg) + promethazine (25-50 mg mix).
- 4 h later, equal numbers in both groups were tranquil or asleep.
- 76% given the haloperidol-promethazine were asleep compared with 45% of those on lorazepam (RR=2.29, 95% CI 1.59-3.39; NNT=3.2, 95% CI 2.3-5.4). The haloperidol-promethazine mix produced a faster onset of tranquillisation/sedation and more clinical improvement over the first 2 h.
- Neither intervention differed significantly in the need for additional intervention or physical restraints, numbers absconding, or adverse effects.

A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis.

- 172 patients, practical clinical trial, haloperidol (N = 56), risperidone (N = 61), and olanzapine (N = 55). Mean modal daily doses were 5.4 mg/day for haloperidol, 4 mg/day for risperidone, and 15.3 mg/day for olanzapine; 98.3% of subjects were drug naive at baseline.
- All 3 treatments showed similar effectiveness in reducing the severity of general, negative, and positive sx after 6 weeks. No statistical differences among groups.
- Extrapyramidal symptoms and concomitant anticholinergic medication use was greater with haloperidol than olanzapine or risperidone.
- Olanzapine-treated patients had significantly more weight gain vs haloperidol and risperidone groups.

Haloperidol for psychosis-induced aggression or agitation (rapid tranquillization)

• 32 studies comparing haloperidol with 18 other treatments.
• Few studies reflect real world practice, most were small and carried considerable risk of bias.
• Haloperidol > placebo: asleep at two hours (2 RCTs, n = 220, risk ratio (RR) 0.88, 95% confidence interval (CI) 0.82 to 0.95). Dystonia was common (2 RCTs, n = 207, RR 7.49, CI 0.93 to 60.21).
• Three trials (n = 205) compared haloperidol vs lorazepam. There were no significant differences between the groups with regard to the number of participants asleep at one hour.
Rapid tranquilization of severely agitated patients with schizophrenia spectrum disorders: a naturalistic, rater-blinded, randomized, controlled study with oral haloperidol, risperidone, and olanzapine

- 43 severely agitated patients at acute care psychiatric units
- randomly assigned to receive either daily haloperidol 15 mg, olanzapine 20 mg, or risperidone 2 to 6 mg over 5 days.
- All drugs were effective for rapid tranquilization within 2 hours. Over 5 days, the course differed between agents (P < 0.001), but none was superior.
- Dropouts occurred only in the risperidone and olanzapine groups.

Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses

- 4 trials **olanzapine IM vs. IM placebo** (total n=769, 217 placebo).
- olanzapine IM > placebo at 2 hours (4 RCTs, n=769, RR 0.49 CI 0.42 to 0.59, NNT 4 CI 3 to 5) and olanzapine IM was as acceptable as placebo.
- olanzapine IM did not seem associated with extrapyramidal effects.
- 2 trials **olanzapine IM vs haloperidol IM** (total n=482, 166 allocated to haloperidol). No differences between olanzapine IM and haloperidol by 2 hours for the outcome of 'no important clinical response'.
- 2 trials compared **olanzapine IM with lorazepam IM** (total n=355, 119 allocated to lorazepam). For the outcome of 'no important clinical response', there was no difference at 2 hours.
- No studies reported outcomes related to hospital and service use, satisfaction with care or suicide, self-harm or harm to others.
- No studies evaluated the oro-dispersible form of olanzapine.

Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses

• “Data relevant to the effects of olanzapine IM are taken from some studies that may not be considered ethical in many places, all are funded by a company with a pecuniary interest in the result. These studies often poorly report outcomes that are difficult to interpret for routine care. Other important outcomes are not recorded at all.”

Loxapine - Cochrane review (2007)

- 41 studies
- Compared with placebo, loxapine has an antipsychotic effect (Global effect - not improved at six weeks: n=78, 2 RCTs, RR 0.30 CI 0.1 to 0.6 NNT 3 CI 3 to 5).
- As effective as typical drugs in the short term (4 -12 weeks) (Global effect: n=580, 13 RCTs, RR 0.86 CI0.7 to 1.1; mental state: n=915, 6 RCTs, RR 0.89 CI 0.8 to 1.1).
- Very limited heterogeneous data suggest that, given intramuscularly (IM), loxapine may be at least as sedating as IM haloperidol and thiothixene (Navane).
- Loxapine is also as effective as atypicals (risperidone, quetiapine) (n=468, 6 RCTs, RR mental state not improved 1.07 CI 0.8 to 1.5).
- Adverse effect profile is similar to typicals - more extrapyramidal adverse effects when compared with atypical (n=340, 4 RCTs, RR 2.18 CI 1.6 to 3.1).
Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine

Michael D. Lesem et al. BJP 2011;198:51-58

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Loxapine - Results and limitations

• Loxapine is FDA approved for the acute treatment of agitation associated with schizophrenia or bipolar disorder in adults

• 18 sites to recruit 129 patients over a year and half (7.2pts/site)

• Pts needed to be able to read and provide informed consent, to understand and follow technique for device

• Bronchospasm is a black box warning and that there is a Risk Evaluation and Mitigation Strategy (REMS) to assess prior to prescribing and monitoring the patient after each administered dose.
Loxapine - Results and limitations - II

• The people who need this medication are generally medically complex, may have street drugs in their system, are generally cigarette smokers and their pulmonary and in many cases their cardiac status may be unknown. If the initial dose is not effective, the question becomes - now what?

• It can only be given in a registered health care facility by personnel who can assess and manage any pulmonary complications.

• 60 capsules of loxapine 10mg (generic) $32.84

• average wholesale price for ONE 10-mg package of Adasuve $145 -> often not on formulary
Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside A Randomized, Double-blind, Placebo-Controlled Trial

• Single low-dose sodium nitroprusside IV (0.5 μg/kg/min for 4 hours) to 20 patients with schizophrenia taking antipsychotics

• Outcome: changes in positive, negative, anxiety, and depressive symptoms during the following 4 weeks.

• (0.5 to 10 μg/kg/min dose rates for hypertension)

• Mechanism? modulate the NMDA–nitric oxide–cGMP pathway

Mean Total 18-Item Brief Psychiatric Rating Scale Scores

A, Scores during the first 12 hours; B, scores at 4 weeks. Asterisks indicate statistically significant P values as given in the text; error bars, SEMs.
Let’s talk about ECT
1) it works

• Meta-analysis, the overall remission rate was 50.9% (n = 402/790) for patients with MDD and 53.2% (n = 168/316) for patients with BP dep. (Dierckx B. Bipolar Disord. 2012)

• 73 patients with BP-TRD. ECT (3x wk, RUL, brief) vs algorithm-based pharmacological treatment.

• Response significantly higher in the ECT group (73.9% versus 35.0%), but the remission rate did not differ between the groups (34.8% versus 30.0%).

2) it’s fast

• Depressed patients often begin to respond after the first treatment and progress to remission with 6 to 12 treatments.

• There is **considerable variability** in the trajectories, somatic symptoms usually improve first.

• Patients who respond early in a course of ECT have a greater likelihood of ultimately achieving remission.

How fast is ECT really?

• In a study carried out by the Consortium for Research in ECT (CORE) 34% of 253 patients achieved remission (HAM-D score of 10) at or before the 6th session with ECT (within 2 weeks) and 65% achieved remission at or before the 10th session (within 3 to 4 weeks).

• 54% had an initial first response (decrease of 50% in HAM-D score) by session 3.

• Furthermore, 19% of the seriously ill cohort in this study (baseline HAM-D score of approximately 35) experienced remission with 4 or fewer ECT sessions.

How fast is ECT? II

• Need to balance speed of response to ECT in major depression and adverse cognitive effects

• Speed of response was significantly greater with ECT x 3/wk but this schedule induced more severe memory impairment, even when the number of ECT in the series was not significantly different between the two groups.

Cranial Electric Stimulation

  - 120 antidepressant-free patients with moderate to severe, nonpsychotic, unipolar MDD
  - Six-week treatment of 2-mA anodal left/cathodal right prefrontal tDCS and sertraline (50 mg/d)
- Barclay and Barclay. A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. Affect Disord. 2014
  - N= 115, primary diagnosis of an anxiety disorder
  - all intakes were performed at the principal investigator’s private practice location.
Cranial Electric Stimulation – at MGH

- Efficacy and safety of a form of cranial electrical stimulation (CES) as an add-on intervention for treatment-resistant major depressive disorder: A three week double blind pilot study. Mischoulon et al. J Psychiatr Res. 2015
  - Thirty subjects (57% female, mean age 48.1 ± 12.3 years)
  - randomized to 3 weeks of treatment with CES (15/500/15,000 Hz, symmetrical rectangular biphasic current of 1-4 mAmp, 40 V) or sham
  - Both treatment groups demonstrated improvement of about 3-5 points in HAM-D-17 scores (p < 0.05 for both), and no significant differences were observed between groups. Remission rates were 12% for CES, and 15% for sham
A two-site pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients.

- 2-site, randomized, active sham-controlled (1:1)
- 9 sessions of rTMS over 3 days as adjunctive to usual inpatient for suicidality treatment. The setting was two inpatient military hospital wards (one VA, the other DOD).
- screened approximately 377 inpatients, yielding 41 adults. Comorbid PTSD, TBI or both
- SSI scores declined rapidly over the 3 days for both groups (sham change -15.3 points, active change -15.4 points), with a trend for more rapid decline on the first day with active rTMS (sham change -6.4 points, active -10.7 points, P = 0.12). T

Efficacy and Safety of Low-field Synchronized Transcranial Magnetic Stimulation (sTMS) for Treatment of Major Depression.

• Six-week double-blind sham-controlled treatment trial of a novel device - low-field magnetic stimulation synchronized to an individual's alpha frequency

• 202 subjects comprised the intent-to-treat (ITT) sample, and 120 subjects completed treatment per-protocol (PP).

• There was **no difference** in efficacy between active and sham in the ITT sample.

Low-field Magnetic Stimulation (LFMS) for Treatment of MDD: results from RAPID trial

- 85 subjects in the intent-to-treat (ITT) sample.
- 6 sites, used SPCD design (improvement in depression scores was 1.6 points on the HAMD-17 in the second stage of the study after the placebo responders had been removed), MADRS>=20
- There was **no difference** in efficacy between active and sham in the ITT sample at 48 hrs

Fava et al, presented at ASCP Scottsdale AZ June 2016
Adjunctive triple chronotherapy (combined total sleep deprivation, sleep phase advance, and bright light therapy) rapidly improves mood and suicidality in suicidal depressed inpatients: an open label pilot study. (Sahlem et al, J Psychiatr Res. 2014 Dec;59:101-7)

- 10 participants one night of total sleep deprivation (33-36 h), followed by a three-night sleep phase advance + 4x30-min sessions of bright light therapy (10,000 lux).
- HAMD17 scores dropped from a mean of 24.7 ± 4.2 SD at baseline to a mean of 9.4 ± 7.3 SD on day five (p = .002), 6/10 meeting criteria for remission.

The day-to-day acute effect of wake therapy in patients with major depression using the HAM-D6 as primary outcome measure: results from a randomised controlled trial. (Martiny et al. PLOS one 2013 Jun 28;8(6):e67264)

- Randomized N=36 to sleep deprivation, N=38 to daily exercise
- Patients in the wake therapy group had an immediate, and statistically significant better antidepressant effect with response rates at day 5 of 75.0%/25.1%
Sleep deprivation II

• Over 80 studies involving nearly 2000 patients, SDT robustly and rapidly (within 24–48 h) alleviates symptoms in 40–60% of patients with moderate to severe depression.

• SDT alone offers rapid but short-lasting improvement with relapses frequently associated with recovery sleep.

• Bright light, sleep-phase advance (SPA) can sustain improvement.
Sleep deprivation III

- necessarily single blind..
- How practical is for outpatients? Especially if they are trying to hold onto a job..
- Short duration of effect
- Risk for switch in BP
A Preliminary, Open Study of the Combination of Fluoxetine and Desipramine for Rapid Treatment of Major Depression

- 14 inpatients, responses were retrospectively compared with those of 52 inpatients treated with desipramine alone.
- One week after treatment began, the mean change in Hamilton Depression Rating Scale scores was 42% in the group that received Fl+D and 20% in the group that received D alone (Mann-Whitney U Test, \( P = .007 \)).
- At 2 weeks, the mean change in scores of the group that received Fl+D was 60%, while a 30% change was noted in the patients treated with D alone (\( P = .001 \)).
- 10/14 patients remitted

How about augmenting agents for depression? (2016)

Augmentation with

• Aripiprazole
• Quetiapine
• Stimulants/modafinil
• Pramipexole
• Lamotrigine
Antidepressant response to aripiprazole augmentation associated with enhanced FDOPA utilization in striatum: a preliminary PET study

• (PET) with the DOPA decarboxylase substrate 6-[18F]-fluoro-3,4-dihydroxy-L-phenylalanine (FDOPA), which has been used extensively for imaging of the presynaptic dopaminergic system in brain.
• 14 depressed patients, who had failed 8 weeks of antidepressant therapy with SSRI, underwent FDOPA PET scans before and after aripiprazole augmentation; 11/14 responded to augmentation.
• PET showed increased FDOPA trapping in the right medial caudate of augmentation responders

A randomized controlled trial of the efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with residual symptoms of MDD after treatment with escitalopram

- 8 weeks of open-label escitalopram, randomized to 6 weeks of lisdexamfetamine dimesylate (20-50 mg/d) or placebo augm.
- 129 pts
- Lisdexamfetamine dimesylate augmentation reduced depressive symptoms in participants with inadequate escitalopram response.

Open-Label Study of Minocycline (150 mg/day) as Adjunctive Therapy for Patients with Unipolar Psychotic Depression (n=25)

Fig. 1. HAM-D total score at each assessment from baseline to week 6 (ITT, LOCF).

Citalopram, methylphenidate, or their combination in geriatric depression: a randomized, double-blind, placebo-controlled trial.

- 16 weeks of double blind, randomized to Cit (20-60mg) +pbo, MPH+pbo or cit+MPH
- 143 pts
- All groups showed significant improvement in depression severity and in cognitive performance.
- Improvement in depression severity was more prominent in the cit+MPH group compared with the other two groups.
- The rate of improvement in the cit+MPH group was significantly higher in the first 4 weeks of the trial.

A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of MPH in outpatients with treatment-resistant depression.

• 4-week, randomized, double-blind, MPH (18-54mg) -60 pts
• no statistically significant differences.
• HAM-D21 improvement scores (drug, -6.9; placebo, -4.7).
• Responders were MPH group (40.0%) vs placebo group (23.3%).

A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of MPH in outpatients with treatment-resistant depression.

How do you explain it?

• Duke, academic medical center -
• 70% failed multiple AD trials
• the proportion of responders in each stage of treatment resistance

Responders by stage of TRD: In the drug group, 50% in stage 1, 36% in stage 2, and 25% in stage 3 of participants showed a response compared with 34% in stage 1, 20% in stage 2, and 0% in stage 3 considered as responders in the placebo group.

How about lamotrigine augmentation in MDD?

Barbee et al, J Clin Psychiatry 2011; 72(10):1405-1412

Double-Blind Study of Lamotrigine (up to 400 mg/day) Augmentation of Paroxetine in TRD Patients (n=96)
Riluzole

• open-label study of riluzole monotherapy for patients with TRD ($n=19$) found that riluzole resulted in significant improvement in depression (Sanacora et al. Biol Psych 2007)
• 104 patients with treatment resistant depression
• riluzole (50mg BID) or placebo in a 56-day study that utilized SPCD.
• low placebo response rate (<30%), riluzole did not outperform placebo on mean change in MADRS scores ($p=0.83$). (Sanacora et al. submitted)
Scopolamine

- Centrally acting competitive inhibitor of the muscarinic cholinergic receptor, minimal effects on nicotinic receptors.
- **selectivity for muscarinic receptors, high potency for all five muscarinic receptor subtypes**, slow dissociation rate from central muscarinic cholinergic receptors, and rapidly entering brain
- Currently used for post-operative nausea, GI disorders, motion sickness
- Among the TCAs, AMT has the highest potency for muscarinic receptors, affinity for muscarinic receptors that is similar in magnitude to its affinity for monoamine transporters. At therapeutic doses of AMT, most of the serotonin transporter sites are occupied, as well as a large proportion of muscarinic sites
Scopolamine II

• *Furey and Drevets (Arch Gen Psych 2006)* double-blind, randomized, placebo-controlled crossover, 18 depressed patients: 9 with MDD and 9 with BD. 3 infusions of scopolamine 4.0 µg/kg (3–5 days apart). All patients demonstrated at least a partial response, and 10 patients experienced remission. No patients experienced mania.

• Dose-finding study on 8 MDD patients, random, double-blind, 15-minute IV infusion of saline placebo or scopolamine: 2.0, 3.0, and 4.0 µg/kg.

• mean change in MADRS score between baseline and session 4 was $-13.8 \pm 7.7$ (p<.002). Five subjects showed a >50% reduction in the MADRS score, and three remitted (MADRS< 10).
Drevets and Furey (Biol Psych 2010), another double-blind, randomized, placebo-controlled crossover study, 22 MDD. The scopolamine group had a 32% reduction in MADRS scores, compared with a 6.5% reduction in the placebo group. The effect persisted for 12 to 16 days after the final scopolamine infusion. Eleven patients experienced remission.


Khajavi 2012, 40 pts with MDD oral scopolamine (1mg) as augmentation of citalopram, higher response rate (65% vs 30%) at wk 6.
Scopolamine - IV

- AEs: Blurred vision, dry mouth, light-headedness, transient (2 - 4 hours)
- No subject developed delirium, psychosis, overt confusion, clinically significant cardiovascular effects, or treatment-emergent suicidal ideation
- No subject developed hypomania.
- Relief from depressive symptoms on the first morning after scopolamine infusion
Antidepressant Efficacy of Scopolamine (4 mcg/Kg)

A

Baseline Assessments

MADRS Score

P<.05

Furey and Drevets, Arch Gen Psychiatry. 2006;63:1121-1129
Scopolamine mechanisms?

- NMDAR gene expression is enhanced by muscarinic receptor stimulation in at least some brain structures.
- Li et al (Science 2010) reported that ketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway, leading to increased synaptic signaling protein expression and increased number and function of new spine synapses in the rodent prefrontal cortex.
- Blockade of mTOR signaling interrupted ketamine induction of synaptogenesis and the associated antidepressant-like, behavioral responses in rodent models.
- The same group demonstrated that scopolamine also induces the mTOR pathway at a timing and magnitude similar to ketamine (Neuroscience Meeting presentation 2011).
A single dose of ketamine IV improved depressive symptoms within 72 hours (n=7 -TRD) (Berman, Biol. Psychiatry, 2000).

Zarate et al. : double-blind, placebo-controlled, crossover study: single ketamine infusion had fast and sustained antidepressant effects in 17 patients with TRD (Arch General Psychiatry 2006).

- 71% of subjects were improved 24 hrs after infusion.

-Replicated in other samples in patients with MDD and BP depression
Ketamine Mechanism(s) of action

Increase glutamate transmission, increase synaptogenesis

Adapted from Duman et al., Science, 2012
Ketamine Mechanism(s) of action - II

- Neurobiological mechanisms of ketamine’s antidepressant actions are more complex than NMDA receptor blockade.
- primary mechanism of action is blockage of the NMDA receptor at the PCP site within the ionotropic channel.
- -> disinhibition of GABAergic inputs and enhancing the firing rate of glutamatergic neurons, increases the presynaptic release of Glu
- This increase in Glu release then preferentially favors AMPA receptors over NMDA receptors because the latter are blocked by ketamine
- The net effect of ketamine on a cellular level is an increased glutamatergic throughput of AMPA relative to NMDA
- increased glutamatergic activity (Maeng et al. Biol. Psychiatry, 2008)
Ketamine Safety and tolerability

• Moderate anxiety, irritability, headache, increased libido.
• Analgesia, anesthesia, brief hyper- or hypotensive episodes, tachycardia or bradycardia, bradypnea (aan het Rot et al. Biol. Psychiatry, 2010).
• Most adverse effects peaked within 40 minutes and ceased within 80 minutes post-infusion (Zarate et al., 2006).
Ketamine Safety and tolerability

- 205 intravenous (IV) ketamine infusions (0.5 mg/kg over 40 minutes) in 97 participants with DSM-IV-defined major depressive disorder (MDD) pooled from 3 clinical trials
- Overall antidepressant response rate, (≥ 50% improvement in MADRS), was 67%.
- 4 of 205 infusions (1.95%) were discontinued due to AEs. The overall attrition rate was 3.1%.
- In the first 4 hours after the infusion, the most common general AEs were drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. Approximately one third of individuals experienced protocol-defined hemodynamic changes.
- No cases of persistent psychotomimetic effects, adverse medical effects, or increased substance use in a subgroup of patients with available long-term follow-up information.

Ketamine vs. Placebo in Unipolar and Bipolar Depression

Major depression

Bipolar depression

†P < 0.001; ‡P < 0.01; and *P < 0.05.

Dotted Line = Placebo
Solid Line = Ketamine


Courtesy Dr Ionescu
Ketamine vs. Midazolam in TRD

![Graph showing comparison between Ketamine and Midazolam in TRD treatment.](graph.png)

Murrough et al, Amer J Psych. 2013

Courtesy Dr Ionescu

p≤0.02;
Ketamine vs. Midazolam in TRD

Response Rate (%)

Day 1 | Day 2 | Day 3 | Day 7

Ketamine (N=47) | Midazolam (N=25)

Courtesy Dr. Ionescu

Murrough et al, Amer J Psychiat 2013
Ketamine and suicide

• Price et al: patients with TR MDD have reduced MADRS suicide subscale scores 24 hrs after a single ketamine infusion (n=26, Biological Psychiatry, 2009).

• DiazGranados et al: 33 patients with TRD received a single ketamine infusion: suicidal ideation scores decreased at 40 minutes, remained significantly decreased for 4 hours (Journal of Clinical Psychiatry, 2010).

• Larkin et al. reported similar findings in an emergency room setting in patients with depression and SI. Patients received single ketamine bolus, with changes in MADRS scores at 40 minutes that persisted 10 days. (n=14, open-label, Int. Journal of Neuropsychoph 2011).
Ketamine and suicide II

• Murrough et al. *Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial.* (Psychol Med 2015 Dec;45(16):3571-80.)

• randomized, controlled trial, N=24 patients with mood and anxiety spectrum disorders with clinically significant SI, single infusion of ketamine or midazolam

• SI measured using the Beck Scale for Suicidal Ideation (BSI) 24 h post-treatment represented the primary outcome

• BSI score was not different between the treatment groups at 24 h (p = 0.32); however, a significant difference emerged at 48 h (p = 0.047). MADRS-SI score was lower in the ketamine group compared to midazolam group at 24 h (p = 0.05). The treatment effect was no longer significant at the end of the 7-day.
Ketamine in PTSD

- randomized, double-blind, crossover trial ketamine vs midazolam
- 41 pts with PTSD, free of concomitant psychototropic medications for 2 weeks - 29 of them completed both infusions and ratings
- Significant and rapid reduction in PTSD symptom severity at 24 hours after infusion
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketamine(^a) (n = 22)</th>
<th>Midazolam(^b) (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>36.4 (10.8)</td>
<td>35.7 (10.0)</td>
</tr>
<tr>
<td>Female, sex, No. (%)</td>
<td>13 (59.1)</td>
<td>6 (31.6)</td>
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<td>Race, No. (%)</td>
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<td>11 (50.0)</td>
<td>12 (63.2)</td>
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<tr>
<td>White</td>
<td>5 (22.7)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (27.3)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Hispanic ethnicity, No. (%)</td>
<td>5 (22.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Education,(^c) No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤High school</td>
<td>1 (4.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>3 (14.3)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Some college</td>
<td>12 (57.1)</td>
<td>14 (73.7)</td>
</tr>
<tr>
<td>≥4 Years of college</td>
<td>5 (23.8)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Unemployed, No. (%)</td>
<td>11 (50.0)</td>
<td>14 (73.7)</td>
</tr>
<tr>
<td>Married or cohabiting, No. (%)</td>
<td>5 (22.7)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Primary trauma, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual assault or molestation</td>
<td>9 (40.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Physical assault or abuse</td>
<td>4 (18.2)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Accident or fire</td>
<td>1 (4.5)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Combat exposure</td>
<td>2 (9.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Witnessed violent assault or death</td>
<td>4 (18.2)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Witnessed 9/11 terrorist attacks</td>
<td>2 (9.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Duration of PTSD, mean (SD), y</td>
<td>14.2 (12.3)</td>
<td>11.9 (14.0)</td>
</tr>
<tr>
<td>History of treatment with psychotropic medication, No. (%)</td>
<td>11 (50.0)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>CAPS score (past month), mean (SD)</td>
<td>82.5 (14.1)</td>
<td>77.1 (11.8)</td>
</tr>
<tr>
<td>QIDS-SR score, mean (SD)</td>
<td>12.4 (5.2)</td>
<td>11.3 (5.6)(^d)</td>
</tr>
</tbody>
</table>

\(^a\)Ketamine \(n = 22\), \(^b\)Midazolam \(n = 19\), \(^c\)Education level \(≤\) high school: some college or higher, \(^d\)QIDS-SR score was not available for one subject in the Ketamine group.
Ketamine studies at MGH

- Ketamine as ADD-on to treatment-as-usual
- OPEN –LABEL
- 14 depressed patients very treatment-resistant with suicidal ideation
- 6 infusions of ketamine over 3 weeks.
- Escalating dose if no response
- 5 patients out of 12 completers (41.7%) were responders, and 2 out of 12 were in remission (16.7%).
- 5/12 had no suicidal ideation
- Response lasted approximately 2-3 weeks
Repeated-Dose Ketamine for Suicidal Ideation

CSSRS-Ideation Score

Time

Baseline (n=14) Infusion 1 (n=14) Infusion 2 (n=14) Infusion 3 (n=13) Infusion 4 (n=13) Infusion 5 (n=12) Infusion 6 (n=12)

Ionescu et al, J Clin Psych 2015
How to sustain the effect of ketamine?

- Riluzole, lamotrigine did not work
- Multiple doses (MGH), different doses
- BIW vs TIW no difference (Singh et al 2016)
- Possibly lithium in BP depression

- Needs to be continued...
- $$, not practical
The search for ketamine-like
AZ 6765 (lanicemine)

- 22 medication-free pts with TRD, single infusion of lanicemine 150mg significantly reduced depression scores within 80 minutes
- 34 pts with MDD ($n=34$) randomized to single infusion of lanicemine 100mg vs placebo. Change in MADRS scores at 24 hrs did not differ significantly from placebo. Placebo response was an average of more than 14 points
The search for ketamine-like: AZ 6765 (lanicemine)

- 125 medicated patients with MDD randomized to repeat infusions of adjunctive lanicemine 100 mg, 150 mg, or placebo – both doses efficacious
- Large multi-site trial was negative, as the placebo response rate was 39% at primary endpoint
- AZ shut down the pipeline
The search for ketamine-like: RG7090 Basimglurant (Roche)

- Selective metabotropic glutamate subtype 5 (mGlu5) receptor–negative allosteric modulator
- Colocalized and functionally interacting with NMDA receptors by potentiating NMDA-induced currents in the brain
- 333 pts, 59 sites, as adjunctive of TAU (1-3 failed AD)
- The placebo group had a 14.6-point reduction on the MADRS, and 46.8% of the participants assigned to placebo experienced a response by week 6.
- Unique subjective effects associated with this novel class of medications may not be appreciated by measures such as the physician-rated MADRS

The search for ketamine-like: 
**CP-101,606 Traxoprodil (Pfizer)**

- R2B subunit-selective N-methyl-D-aspartate receptor antagonist
- Pts failed 1-3 failed AD
- 6-week open-label trial of paroxetine and a single-blind, intravenous placebo infusion. Period 1 nonresponders (n = 30) then received a randomized double-blind single infusion of CP-101,606 or placebo
- Significant antidepressant effect ➔ 8.4-point greater reduction in the MADRS score in patients receiving CP-101,606 versus those receiving placebo
The search for ketamine-like: CP-101,606 (Pfizer)

- 1272 went through a thorough screening via telephone, 192 went through a face-to-face interview to yield a total of 47 patients who were entered to period 1. A total of 30 subjects (15 subjects per group) were randomized to period 2.
- 17 responded to single blind placebo (36%)

- How generalizable the results in this sample?
The search for ketamine-like: CERC-301 (MK-0657) (Cerecor)

- NR2B selective NMDA-antagonist
- randomized, double blind, placebo-controlled crossover study, oral
- no significant differences (p=0.27) in antidepressant efficacy were found between MK-0657 and placebo on the primary outcome measure
- 5 patients (out of the 21 planned) completed both periods of the crossover portion of the study (in part due to recruitment challenges and discontinuation of the compound by the manufacturer).
- Still in development
The search for ketamine-like: 
Rapastinel (Glyx-13)

• functional partial agonist at the glycine-binding site on the NMDA receptor
• randomized, double-blind trial \((n=116)\) with MDD, failed 1 AD, rapastinel (at doses 1, 5, 10, or 30 mg/kg) or placebo.

• Long-term safety and efficacy research is ongoing. Rapastinel has received the FDA’s breakthrough therapy designation
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The search for ketamine-like: Dextromethorphan combos

- **AVP-786 (dextromethorphan/quinidine)** Avanir
  - Noncompetitive NMDA receptor antagonist, as well as a sigma-1 receptor agonist
  - Results of clinical trial pending
- **AXS-05 (dextromethorphan/bupropion)** Axsome
  - Currently in Phase III
Bridging clinic and research

- About 60 ketamine clinic in USA, fee for service
- At MGH we opened a ‘ketamine clinic’ using IN ketamine for TRD
- Patients involved in research, in their own monitoring (“stakeholders”), in identifying augmentations and interactions of concomitant drugs
- Ketamine responders and non responders in clinical trials of new compounds