EPA Administrative Office
15 avenue de la Liberté
67000 Strasbourg – FRANCE

Phone +33 388 239 930
Fax +33 388 352 973

EPA Brussels Office
University Foundation
11 rue d'Egmont
1000 Brussels – BELGIUM

www.europsy.net

Ketamine in psychiatric treatment and research

Position Statement of the European Psychiatric Association (EPA)

25 February 2015

The European Psychiatric Association (EPA) represents over 78 500 individual psychiatrists and 37 National Associations of Psychiatry from across Europe.

Introduction

Ketamine is a widely used anesthetic medication that has gained growing importance for human suffering through the alleviation of pain and the treatment of mood disorders. Because it is easy to use and inexpensive, ketamine is one of the most commonly used anesthetic agents in developing countries[1]. More than 50 years of experience suggests that ketamine is safe and well tolerated.
There is large body of scientific evidence regarding ketamine's efficacy and safety in the treatment of people with unipolar and bipolar depression, and suicidality. Ketamine is also a valuable tool in the research of mental disorders.
The Commission on Narcotic Drugs, 58th Session, has been asked to review a proposal to place ketamine in Schedule I of the 1971 Convention (E/CN.7/2015/7[2] and E/CN.7/2015/8[3]).
The WHO Expert Committee on Drug Dependence (ECDD) critically evaluated ketamine in 2006, 2012 and 2014. Based on accumulated evidence and data on non-medical use, diversion and trafficking, and evidence of ketamine's therapeutic value, the ECDD does not recommend that the CND place ketamine under international control.[2]
A wide range of national and international organizations, including medical and scientific associations have voiced concern about the proposal, including those endorsing the "Fact Sheet on the Proposal to Discuss International Scheduling of ketamine at the 58th CND"[1]. The Fact Sheet provides compelling legal, medical and social arguments against placing ketamine in any schedule of the 1971 Convention. The EPA has endorsed the Fact Sheet.
The EPA would like to provide additional arguments through this Position Statement to emphasize the importance of medical access to ketamine for many people with mental disorders and for research addressing unmet needs in medical care.

The antidepressant effect of ketamine in unipolar and bipolar depression

To our knowledge the first double blind cross-over study in patients with Major Depressive Disorder (MDD) was published in 2000[4]. The authors reported significant improvement within 72 hours in half of the patients. These results were replicated by several other researchers. Further studies provided support for a clinically significant and rapid antidepressant effect of ketamine in bipolar depression[5,6,7,8]. In contrast to standard antidepressants ketamine was not associated with a switch to manic episodes in patients with bipolar depression[9].

Ketamine is effective at rapidly reducing the range of depressive symptoms, including suicidal ideation[10,11,12,13]. The rapid amelioration of suicidal ideation by ketamine is particularly important since current antidepressants are slow to act and have been reported to potentially worsen suicidal ideation in the short-term (see Summary of the Product Characteristics for individual drugs).

Treatment-resistant depression: major indication for ketamine

MDD resistant to standard antidepressant treatment represents one of the most challenging problems in health care. Only 50–60% patients with depression respond to the first antidepressant and only a third of them reach clinical remission[14]. Patients who do not respond to a second antidepressant drug have a very low chance (10–20%) of remission[15]. There is substantial evidence that ketamine is effective for treatment resistant depression[16,17].

Safety of ketamine

Concerns over dissociative and other neurocognitive effects of ketamine, abuse potential and neurotoxic effects of NMDA receptor antagonists shown in rats warrant a cautious approach to the use of ketamine treatment. But more than 50 years of experience with ketamine in clinical practice suggests that ketamine is overall very safe and well tolerated. Although the transient cognitive and dissociative effects of ketamine limit its widespread application in the treatment of depression, it represents an essential addition to the available safe and effective therapeutic options for severe and treatment-refractory cases [16,17,18,19].

Ketamine in research for improved treatment of mental disorders

Modulation of the glutamate system with ketamine bears great potential for the development of innovative new drugs, including antidepressants, as has already been shown in studies with healthy volunteers[20] and clinical trials [21]. Ketamine is currently a very important pharmacological tool for translational research, that is for clinical studies in patients with depression and for preclinical and clinical research models of psychotic disorders, such as schizophrenia[22,23,24,25].

Summary

- Ketamine rapidly reduces core symptoms of depression within 24–72 hours of a single treatment with sub-anesthetic doses.
- Ketamine antidepressant effect is also well documented in treatment-resistant depression. Ketamine has no substitute for this indication at present.
- Ketamine is effective at immediate reducing suicidal ideation.
- Although the transient cognitive and dissociative effects of ketamine limit its widespread use in the treatment of depression, it represents an essential addition to the safe and effective therapeutic interventions for severe and treatment-refractory depression.
- Ketamine is a useful and valid tool in research for the improvement of treatment of mental disorders.

Conclusions

The risk of ketamine addiction arising from the diversion of ketamine from pharmacies does not outweigh the enormous body of data supporting the important and useful medical role for ketamine. Therefore EPA, which has close cooperative relations with national and regional societies of mental health, psychiatry and neuropsychopharmacology is opposing the classification of ketamine as a Schedule 1 drug ("no meaningful medical use").

Prof. Wolfgang Gaebel
EPA President

Prof. Peter Falkai
Chair of the EPA Council of
National Psychiatric Associations

Prof. István Bitter
Chair of the EPA Section of
Psychopharmacology

References:

1. Fact Sheet on the Proposal to Discuss International Scheduling of ketamine at the 58th CND. http://www.bap.org.uk/pdfs/Ketamine_fact_sheet_27-2-2015_EN.pdf Last accessed: 27.02.2015
2. United Nations Economic and Social Council: Changes in the scope of control of substances. E/CN.7/2015/7. Last accessed: 24.02.2015
3. United Nations Economic and Social Council: Changes in the scope of control of substances: proposed scheduling recommendations initiated by the World Health Organization. E/CN.7/2015/8. Last accessed: 24.02.2015
4. Berman, R. M., Cappiello, A., Anand, et al (2000). Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 47: 351-354
5. Diazgranados N, Ibrahim L, Brutsche NE et al. (2010a). A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry. 67: 793-802
6. Zarate CA Jr, Brutsche NE, Ibrahim L (2012). Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry. 71: 939-946
7. Rybakowski JK, Permoda-Osip A, Skibinska M, et al. (2013). Single ketamine infusion in bipolar depression resistant to antidepressants: are neurotrophins involved? Hum Psychopharmacol. 28: 87-90
8. Nugent AC, Diazgranados N, Carlson PJ, et al. (2014). Neural correlates of rapid antidepressant response to ketamine in bipolar disorder. Bipolar Disord.16: 119-128.
9. Niciu MJ, Luckenbaugh DA, Ionescu DF (2013). Subanesthetic Dose Ketamine Does Not Induce an Affective Switch in Three Independent Samples of Treatment-Resistant Major Depression. Biol Psychiatry. 74: e23-e24
10. Murrough JW (2012). Ketamine as a novel antidepressant: from synapse to behavior. Clin Pharmacol Ther. 91: 303–309
11. Larkin GL, & Beautrais AL (2011). A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int J Neuropsychopharmacol. 14: 1127-1131
12. Price RB, Nock MK, Charney DS (2009). Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry. 66: 522-526
13. Price RB, Iosifescu DV, Murrough JW, et al. (2014). Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depression and Anxiety. 31: 335-343
14. Fava M & Davidson K (1996). Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am. 19: 179
15. Rush AJ, Warden D, Wisniewski SR, et al. (2009). STAR*D: revising conventional wisdom. CNS drugs. 23: 627-647
16. Zarate CA Jr, C, Singh J, Carlson P, et al. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 63: 856-86
17. Murrough JW, Perez AM, Pillemer S, et al. (2013). Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 74: 250-256.
18. Murrough JW, Charney DS. (2010). Cracking the moody brain: Lifting the mood with ketamine. Nature Medicine, 16, 1384–1385
19. Sos P, Klirova M, Novak T, et al.(2013). Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. Neuro Endocrinol Lett. 34: 287-293.
20. Höflich A, Hahn A, Kranz GS, et al (2013): Ketamine-induced time-dependent modulation of the thalamo-cortical network in healthy volunteers. Intrinsic Activity, 1(Suppl.1):A4.4
21. Mathews DC, Zarate CA Jr (2013). Current status of ketamine and related compounds for depression. J Clin Psychiatry. 74, 516-517
22. Krystal JH, Karper LP, Seibyl JP (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. **51**: 199–214
23. Anand A, Charney DS, Oren DA (2000). Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Arch Gen Psychiatry. 57: 270-276
24. Bubenikova-Valesova V, Horacek J, Vrajova M, et al (2008). Models of schizophrenia in humans and animals based on inhibition of NMDA receptors. Neurosci Biobehav Rev. 32: 1014-1023
25. Duman RS. (2014). Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. Dialogues Clin Neurosci. 16, 11-27