

SUICIDALITY IN TREATMENT RESISTANT DEPRESSION: PERSPECTIVE FOR KETAMINE USE

Katarzyna Jakuszkowiak-Wojten¹, Maria Gałuszko-Węgielnik¹, Alina Wilkowska¹, Jakub Słupski¹,
Adam Włodarczyk¹, Natalia Górska¹, Joanna Szarmach¹, Łukasz P. Szalach¹, Mariusz S. Wiglusz¹,
Krzysztof Krysta² & Wiesław Jerzy Cubała¹

¹Department of Psychiatry, Faculty of Medicine, Medical University of Gdansk, Gdansk, Poland

²Department of Psychiatry and Psychotherapy, Medical University of Silesia, Katowice, Poland

SUMMARY

Suicidal ideations or attempts in patients with major depressive disorder (MDD) are emergent conditions that require immediate treatment. Numerous therapeutic interventions to reduce suicide risk in psychiatric disorders are effective in long-term suicide prevention, but there is necessity of sufficient, rapid pharmacological treatment of suicidal risk in MDD.

Ketamine, an N-methyl-D-aspartate (NMDA) antagonist, has been reported to have rapid antidepressant effect. Depressive symptoms, anxiety, hopelessness, suicidal ideation had decreased within hours after ketamine infusion. Ketamine's rapid symptoms relief and reduction of suicide thoughts has aroused growing interests in psychiatric association.

Key words: ketamine – NMDA – glutamate - suicidal ideation - depression

* * * * *

INTRODUCTION

Every year some 800 000 people die due to suicide according to WHO (World Health Organization). The neurobiology of suicidal behavior still remains to a large degree unclear. The link between suicide and mental disorders is well established. Depression affects more than 350 million people worldwide (WHO). About 50-60% of patients with MDD fail to achieve remission despite treatment with multiple antidepressants and are considered to suffer from TRD (treatment resistant de) (Fava 2003). Limitations of currently available antidepressant therapies include late -onset response (typically 4-6 weeks), adverse effects and treatment resistance. Difficulties are also associated with treating patients quickly enough to significantly reduce suicidal ideation (Diaz Granados 2010). Rapid antidepressant and anti-suicidal effects of low ketamine doses have been reported since 2000 (Chen 2019). There is a relationship between suicidal ideations and serotonergic, noradrenergic and dopaminergic dysfunctions, however the role of glutamatergic system in suicide has received more attention recent years (Nowak 1995, Zarate 2006, Machado-Vieira 2009, Kalkman 2011, Furczyk 2013, DeLorenzo 2015, Tomassetti 2019).

KETAMINE MECHANISM OF ACTION IN DEPRESSION

The target of majority of conventional antidepressants is monoaminergic system resulting in monoamine amplification. The major biological mechanism of rapid antidepressant ketamine action is different. The process initiated by an N-methyl-D-aspartate (NMDA) antagonist -ketamine in gamma- aminobutric acid interneurons leads to increase synaptogenesis and BDNF (brain-

derived neurotrophic factor) relief (Zarate 2012, Grunebaum 2017, Zanos 2018, Chen 2019). Evidence suggest that low-dose ketamine significantly increases BDNF levels what has been negatively correlated with depression symptoms (Kavalali & Monteggia 2012). However, there are mix findings exploring BDNF levels in anti-suicidal ketamine's effect. Ballard found no correlation between BDNF levels and antisuicidal effects (Ballard 2018). BDNF polymorphism may predict the treatment response of ketamine infusion (Niciu 2017, Chen 2019) Bay-Richter indicated that NMDA receptor antagonists may be effective in suicide and depression due to dys-regulated kynurenine pathway (Bay-Richter 2015).

Ketamine has been widely used in pain management and for induction and maintenance of anesthesia via intravenous or intramuscular administration in many countries since 1970 (Morgan 2012). Ketamine's optimal antidepressant dose in intravenous administration remains unknown. Numerous placebo-controlled studies have demonstrated the ability of ketamine, to induce rapid (within hours), transient antidepressant effects at subanesthetic doses (0.5 mg/kg-1.0 mg/kg over 40 min) (Fava 2019). The infusions of ketamine were relatively well tolerated, except for dissociative symptoms and transient blood pressure elevations with the higher doses, the most common ketamine's adverse effects were headaches and nausea (Singh 2015; Fava 2019). Adverse effects after low doses of ketamine were transient-usually lasted within 30 minutes to 4 hours after administration (Berman 2000, Diazgranados 2010, Zarate 2012, Murrough 2013, Lapidus 2014, Singh 2015, Singh 2016, Daly 2018). It is worth mention, due to its hallucinogenic effect ketamine is used as recreational drug and in larger doses may have addictive properties with its harmful physical and psychological consequences (Curran 2000).

CLINICAL STUDIES REVIEW

Ketamine has shown rapid antidepressant effects many trials in both single and multiple administration (Berman 2000, Zarate 2006, Diazgranados 2010, Zarate 2012, Sos 2013, Murrugh 2013, McGirr 2014, Shiroma 2014, Lapidus 2014, Singh 2015, Loo 2016, Singh 2016, Daly 2018, Mu-Hong Hen 2019). However, repeated ketamine infusions seem to be more beneficial (Zhan Yanni 2019). Ketamine resulted in a rapid anti-suicidal effect in a group of depressed patients with suicidal ideations (Price 2009, Diazgranados 2010, Larkin 2011, Price 2014, Ballard 2015, Ionescu 2016, Bartoli 2017, Grunebaum 2017, Canuso 2018). Some studies (Larkin & Beautrais 2011, Bartoli 2017) showed significant decreased in suicidal ideations score after single ketamine infusion. Study by Grunebaum (2017) reported that ketamine had larger effect on suicidal ideations compared to midazolam. Wilkinson meta-analysis (Wilkinson 2018) of 10 placebo- control randomized trials involving 167 patients with major depressive disorder, bipolar depression and posttraumatic stress disorder revealed that ketamine significantly reduced suicidal ideations in clinician-administrated and self-reported outcomes. In contrast to earlier trials, other studies (Ballard 2018; Ionescu 2019) revealed that patients with long-standing history of chronic SI were less likely to respond to ketamine. The possible explanation is that dose 0.5 mg/kg over 40 minutes was not sufficient in treatment resistant patients and the level of chronicity in these samples were higher than in prior studies (Ballard 2018, Ionescu 2019). Some authors suggested that suicidal ideations response to ketamine occurs partially independently of antidepressant response and can be treated as distinct target what aligns with previous studies (Wilkinson 2018, Grunebaum 2018, Ballard 2018, Zhan 2019). The anti-suicidal response is not entirely driven by the antidepressant effect of ketamine but there are possible other explanations (Zhan 2019) e.g. reduction of anhedonia (Ballard 2017) or decreased nighttime wakefulness in MDD and Bipolar disorder (Vande 2017). Mechanism of anti-suicide ketamine efficacy still remains unclear.

CONCLUSION

Patient with TRD are at risk of suicide. Therefore, there is a significant need to develop novel treatments for the rapid relief of depressive symptoms. The glutaminergic system has recently obtained a particular concern as a potential therapeutic target. There is growing interest in NMDA antagonist- ketamine due to rapid antidepressant and antisuicidal effect of this agent compared to delayed onset of routine methods (Diaz Granados 2010, Bartoli 2015). The bioavailability of ketamine depends on the route of administration (Mathew 2012). The limitation of ketamine for treating depression is due to it requires intravenous administration and hospital setting with appropriate safety monitoring. Esketamine, the S-enantiomer of ketamine was develo-

ped as an intranasal formulation for therapy in treatment-resistant depression (TRD) (Dally 2018; Popova 2018). Intranasal esketamine has regulatory FDA approval for treatment resistant depression since March 2019 and is available in certified clinics.

Acknowledgements:

This work is supported by the Medical University of Gdańsk, Poland (Grant No. ST-02-0039/07/221).

Conflict of interest: None to declare.

Contribution of individual authors:

Katarzyna Jakuszkowiak-Wojten: literature research and analysis, manuscript writing with input of all authors.

Maria Gałuszko-Węgielnik, Alina Wilkowska, Jakub Słupski, Adam Włodarczyk, Natalia Górska, Joanna Szarmach & Łukasz P. Szałach: literature research and analysis.

Mariusz S. Wiglusz & Krzysztof Krysta literature research, manuscript revision.

Wiesław Jerzy Cubała: manuscript revision, language correction.

References

1. Ballard ED, Luckenbaugh DA, Richards EM, Walls TL, Brutsché NE, Ameli R et al.: Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. *J Psychiatr Res* 2015; 68:68-73
2. Ballard ED, Wills K, Lally N, Richards EM, Luckenbaugh DA, Walls T et al.: Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. *J Affect Disord* 2017; 218:195-200
3. Bartoli F, Riboldi I, Crocarno C, DiBrita C, Clerici M, Carra G: Ketamine as a rapid-acting agent for suicidal ideation: a meta-analysis. *Neurosci Biobehav Rev* 2017; 77:232-236
4. Bay-Richter C, Linderholm KR, Lim CK, Samuelsson M, Träskman-Bendz L, Guillemin GJ et al.: A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. *Brain Behav Immun* 2015; 43:110-117
5. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS et al.: Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000; 4:351-354
6. Canuso CM, Singh JB, Fedgchin M, Alphas L, Lane R, Lim P et al.: Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of double-blind, randomized, placebo-controlled study. *American Journal of Psychiatry* 2018; 175:620-630
7. Chen MH, Li WC, Wu HJ, Cheng CM, Li CT, Hong CJ et al.: Antisuicidal effect, BDNF Val66Met polymorphism, and low-dose ketamine infusion: Reanalysis of adjunctive ketamine study of Taiwanese patients with treatment-resistant depression (AKSTP-TRD). *Affect Disord* 2018; 251:162-169

8. Curran HV, Morgan C: Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addiction* 2000; 95:575-590
9. Daly E, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton R et al.: Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression. *JAMA Psychiatry* 2018; 2:139-148
10. Diaz Granados N, Ibrahim LA, Brutsche NE, Franco-Chaves J, Diazgranados N, Cravchik A et al.: Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* 2010; 71:1605-1611
11. Fava M, Freeman MP, Flynn M, Judge H, Hoepfner BB, Cusin C et al.: Correction: Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Mol Psychiatry* 2019. doi: 10.1038/s41380-018-0311-2
12. Fava M: Diagnosis and definition of treatment-resistant depression. *Biol psychiatry* 2003; 53:649-659
13. Furczyk K, Schutová B, Michel T, Thome J & Büttner A: The neurobiology of suicide - A Review of post-mortem studies *J Mol Psychiatry* 2013; 1:2
14. Grunebaum MF, Ellis S, Keilp JG et al.: Ketamine versus midazolam in bipolar depression with suicidal thoughts: A pilot study midazolam-controlled randomized clinical trial. *Bipolar disord* 2017; 19:176-183
15. Ionescu DF, Swee MB, Pavone KJ, et al.: Rapid and Sustained Reductions in Current Suicidal Ideation Following Repeated Doses of Intravenous Ketamine: Secondary Analysis of an Open-Label Study. *J Clin Psychiatry* 2016; 77:719-725
16. Kalkman HO: Circumstantial evidence for a role of glutamine-synthetase in suicide. *Med Hypotheses* 2011; 76:905-907
17. Kavalali ET & Monteggia LM: Synaptic mechanism underlying rapid antidepressant action of ketamine. *American Journal of Psychiatry* 169:1150-1156.
18. Lapidus KA, Levitch CF, Perez AM et al.: A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol Psychiatry* 2014; 76:970-976
19. Larkin GL & Beautrais AL: A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int J Neuropsychopharmacol* 2011; 14:1127-1131
20. Machado-Vieira R, Yuan P, Brutsche N, Diazgranados N, Luckenbaugh D, Manji HK et al.: Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist. *J Clin Psychiatry* 2009; 70:1662-1666
21. Mathew SJ, Shah A, Lapidus K, Clark C, Jarun N et al.: Ketamine for treatment-resistant unipolar depression. *CNS drugs* 26:189-204
22. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW: A systemic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med* 2014; 45:693-704
23. Morgan CJ & Curran HV: Ketamine use: a review. *Addiction* 2012; 107:27-38
24. Morrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM et al.: Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol Med* 2015; 4:3571-80
25. Niciu MJ, Iadarola ND, Banerjee D, Luckenbaugh DA, Park M, Lener M et al.: The antidepressant efficacy of sub-anesthetic-dose ketamine does not correlate with baseline subcortical volumes in a replication sample with major depressive disorder. *J Psychopharmacol* 2017; 31:1570-1577
26. Nowak G, Ordway GA, Paul IA: Alterations in the N-methyl-D-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. *Brain Res* 1995; 675:157-164
27. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P et al.: Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *Am J Psychiatry* 2019; 176:428-438
28. Price RB, Nock MK, Charney DS and Sanjay JM: Effects of Intravenous Ketamine on Explicit and Implicit Measures of Suicidality in Treatment-Resistant Depression. *Biol Psychiatry* 2009; 66:522-526
29. Singh I, Morgan C, Curran V, Nutt D, Schlag A, McShane R: Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight, *Lancet Psychiatry* 2017, 4:419-426
30. Tomasetti C, Montemitro C, Fiengo ALC, Santone C, Orsolini L, Valchera A et al.: Novel pathways in the treatment of Major Depression: focus on the glutamatergic system. *Curr Pharm Des* 2019; 25:381-387
31. Vande VJ, Ballard BD, Luckenbaugh DA, Bernert RA, Richards EM, Park LT et al.: Antisuicidal response following ketamine infusions associated with decreased nighttime wakefulness in major depressive disorder and bipolar disorder. *J Clin Psychiatry* 2016; 78:1068-1074
32. WHO World Health Organization: www.who.int/en/news-room/fact-sheets/detail/depression
33. WHO World Health Organization: www.who.int/health-topics/suicide#tab=overview
34. Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Morrough JW, Feder A et al.: The effect of single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry* 2018, 175:150-158
35. Zanos P, Gould T: Mechanism of ketamine action as an antidepressant. *Mol Psychiatry* 2018; 23:801-811
36. Zarate CA, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A et al.: Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry* 2012; 71:939-946
37. Zhan Y, Zhang B, Zhou Y, Zheng W, Liu W, Wang C et al.: A preliminary study of anti-suicidal efficacy of repeated ketamine infusions in depression with suicidal ideation. *J Affect Disord* 2019; 251:205-212

Correspondence:

Katarzyna Jakuszkowiak-Wojten, MD, PhD
Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk
Dębinki St. 7 build. 25, 80-952 Gdańsk, Poland
E-mail: k.jakuszkowiak@gumed.edu.pl