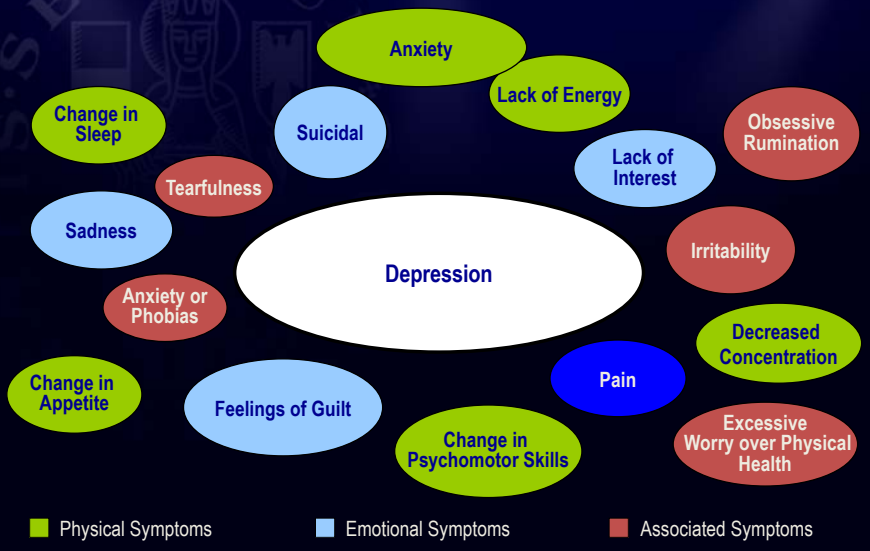
Strategie Farmacologiche con Vortioxetina

Prime Evidenze della Pratica Clinica

Andrea Fagiolini, M.D.

University of Siena

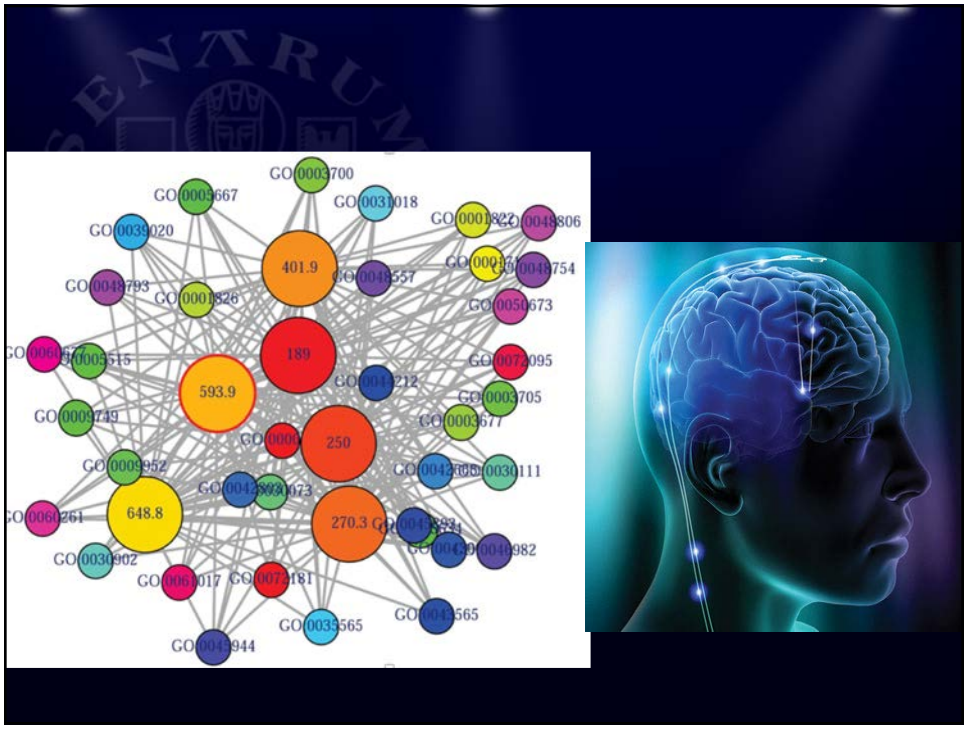
Multidimensional Aspects of Depression



American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, 2000:352.
Ohayon MM, et al. Arch Gen Psychiatry. 2003;60(1):39-47.

Personalized Treatment

Think different.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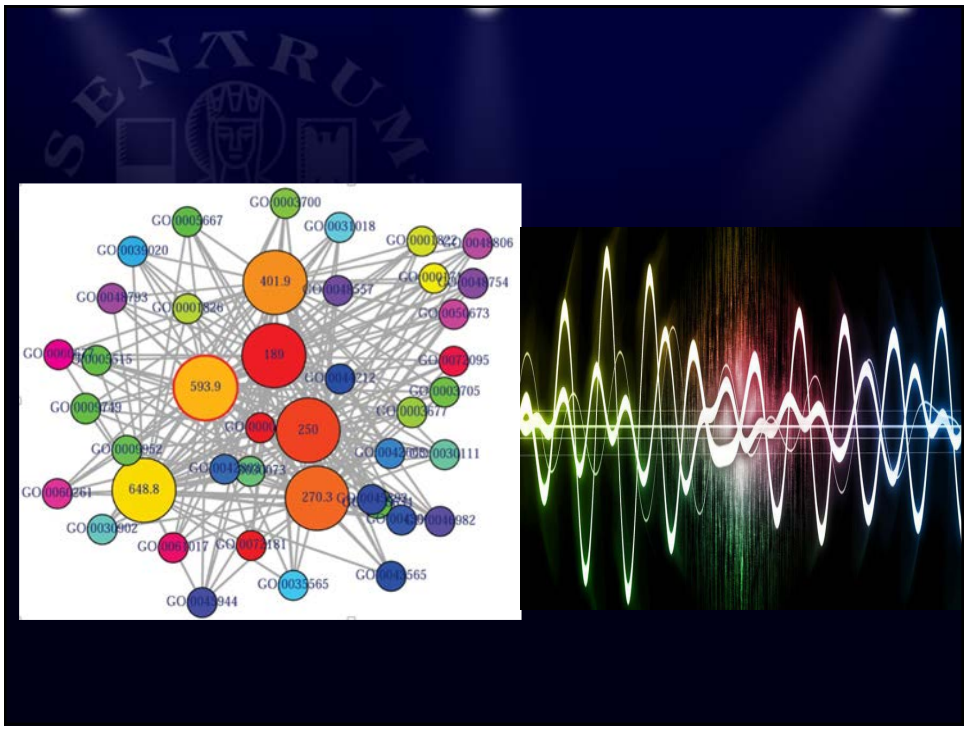
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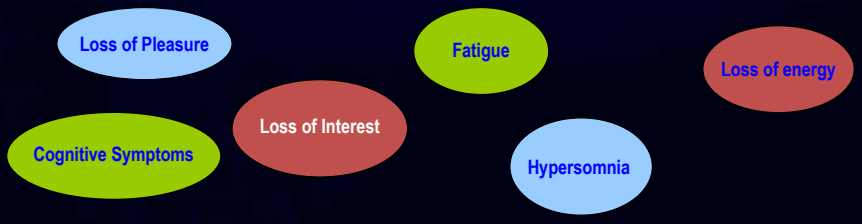
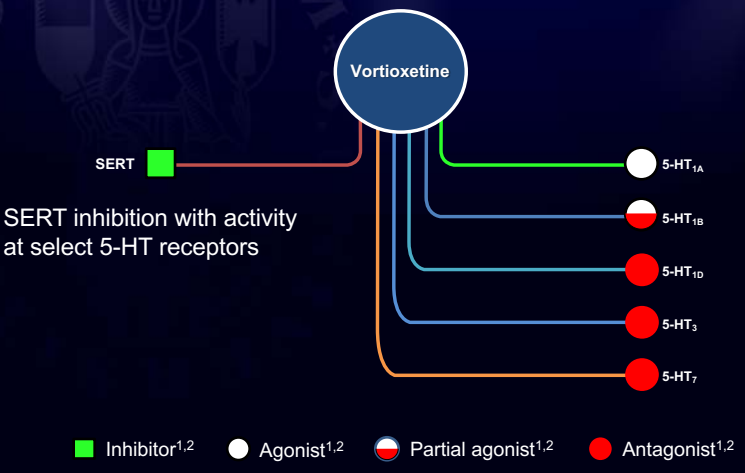
SSRIs UNMET NEEDS

There appears to be a pattern of symptoms that are inadequately addressed by serotonergic antidepressants



Nutt D et al. J. Psychopharm 2007, 21 (5): 461-471

Vortioxetine is a multimodal antidepressant



1. Bang-Andersen B, et al. *J Med Chem*. 2011;54(9)3206-3221;
2. Sanchez C, et al. *Pharmacol Ther*. 2015;145C:43-57.

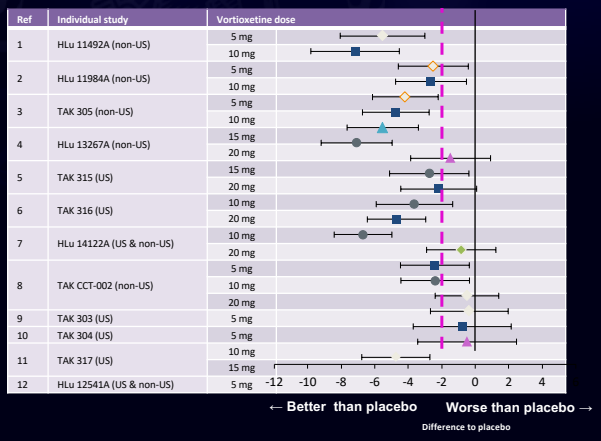
HIGHLIGHTS OF VORTIOXETINE

- Comprehensive clinical development programmes (6700+ patients with depression[1])
- **Effective in a broad range of patient groups, including severe depression, depression and high levels of anxiety, and elderly patients[2–4]**
- In three large, randomised, placebo-controlled trials, vortioxetine improved the cognitive symptoms of depression, as measured by the digit symbol substitution test (DSST)[2,5,6]
- In patients with a suboptimal response to SSRI/SNRI treatment, switching to vortioxetine resulted in a significant improvement in depressive symptoms versus agomelatine[7]
- Vortioxetine is well tolerated[1,14]
  - Adverse events were usually mild or moderate, and occurred within the first two weeks of treatment[1]
  - Comparatively low withdrawal rate due to treatment-emergent adverse events with vortioxetine[14]
  - **Improved sexual functioning in patients experiencing treatment-emergent sexual dysfunction after previous treatment with an SSRI/SNRI*[15]**

1. Baldwin et al. J Psychopharmacol. 2016 Feb 9. pii: 0269881116628440. [Epub ahead of print]; 2. Katona C et al. 2012; 3. Alvarez E et al. 2012; 4. Boulenger JP et al. 2014; 5. McIntyre RS et al. 2014;
6. Mahableshwarkar AR et al. 2015; 7. Montgomery SA et al. 2014; 8. Mørk A et al. 2012; 9. Bang-Andersen B et al. 2011; 10. Guilloux JP et al. 2013; 11. Pehrson AL et al. 2013; 12. Mørk A et al. 2013; 13. Pehrson AL, Sanchez C. 2014; 14. Baldwin DS et al. *Future Neurol*. 2015;10(2); 79–89; 15. Jacobsen PL et al. *J Sex Med*. 2015 doi: 10.1111/jsm.12980

Vortioxetine is effective for the short-term treatment of MDE

Change from baseline in MADRS total score at Week 6/8 (FAS, MMRM)[1–12]

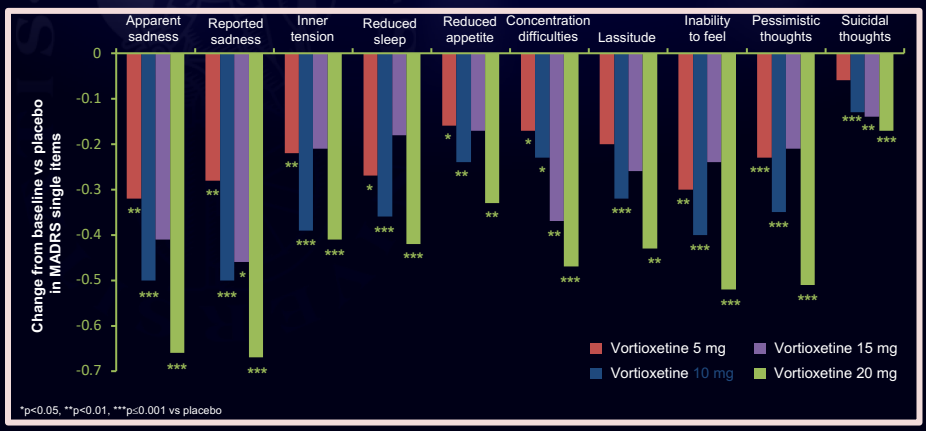


The purple dashed line indicates the target of clinical relevance

- 1. Alvarez E et al. 2012;
- 2. Baldwin DS et al. 2012;
- 3. Henigsberg N et al. 2012;
- 4. Boulenger JP et al. 2014;
- 5. Mahableshwarkar AR et al. 2015;
- 6. Jacobsen PL. *J Clin Psychiatry*. 2015;76:575-582;
- 7. McIntyre RS et al. 2014;
- 8. Vortioxetine EPAR. 2013;
- 9. Jain R et al. 2013;
- 10. Mahableshwarkar AR et al. 2013;
- 11. Mahableshwarkar AR et al. *J Clin Psychiatry*. 2015;76:583-591;
- 12. Katona C et al. 2012

Vortioxetine improves all symptoms of depression as assessed by the MADRS

Meta-analysis of change from baseline in MADRS single items at Week 6/8, difference from placebo – 11 short-term studies in adults (FAS, MMRM)



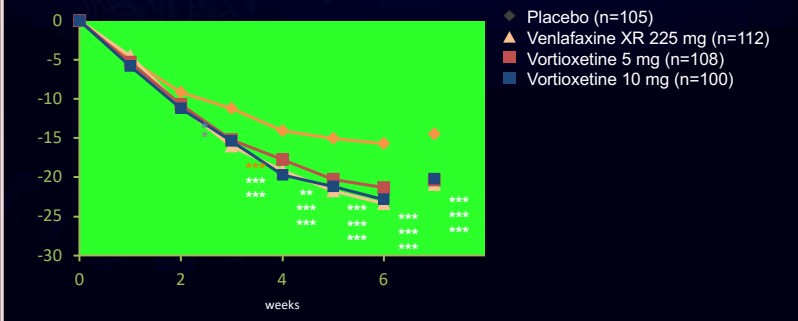
Meta-analysis includes 11 studies: HLu 11492A, HLu 11984A, TAK 305, HLu 13267A, TAK 315, TAK 316, TAK 303, TAK 304, TAK 317, HLu 14122A, and CCT-002
FAS=full analysis set; MMRM=mixed model for repeated measures

1. European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). Vortioxetine. Assessment report for an initial marketing authorisation application. 24th October 2013.
2. Moncrieff J, Kirsch I. Efficacy of antidepressants in adults. BMJ 2005; 331 (7509): 155–157.
3. H. Lundbeck A/S. Vortioxetine, Summary of Product Characteristics. 2013.

Vortioxetine demonstrates efficacy in patients with severe depression

Change from baseline in MADRS total score by visit (FAS, OC, MMRM)1

(FAS, OC, MMRM; endpoint LOCF)



*p<0.05; **p<0.01; ***p<0.001 vs placebo; baseline MADRS total score ≥30

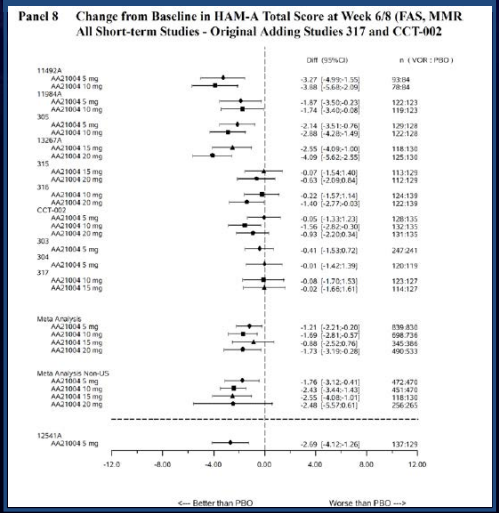
MDD=major depressive disorder; FAS=full analysis set;
MADRS=Montgomery-Åsberg Depression Rating Scale;
OC=observed case; LOCF=last observation carried forward

Alvarez et al. Int J Neuropsychopharmacol 2012;15:589–600

15

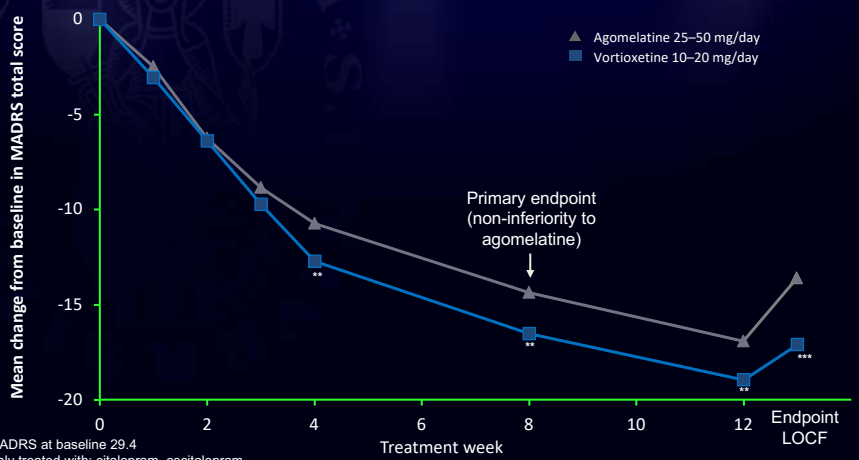
Efficacy in patients with High Anxiety (HAM-A≥20)

MADRS total score: 12 short-term studies in adults with depression and high anxietyWITH



Vortioxetine European Public Assessment Report

EFFECTIVENESS IN NON-RESPONDERS TO SSRI-SNRI*



Mean MADRS at baseline 29.4
*Previously treated with: citalopram, escitalopram, paroxetine, sertraline, duloxetine or venlafaxine

**p<0.01, ***p<0.001 vs agomelatine

Montgomery SA et al. *Hum Psychopharmacol Clin Exp* 2014;29(5):470–482

18

VORTIOXETINE IS EFFECTIVE IN THE TREATMENT OF COGNITIVE SYMPTOMS OF DEPRESSION

A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder

Cornelius Katona[a], Thomas Hansen[b] and Christina Kurre Olsen[b]

International Clinical Psychopharmacology 2012, 27:215–223

A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder

Neuropsychopharmacology (2015), 1–13

Atul R Mahableshwarkar[1], John Zajecka[2], William Jacobson[1], Yinzhong Chen[1] and Richard SE Keefe[*,3]

[1]Takeda Development Center Americas, Deerfield, IL, USA; [2]Department of Psychiatry, Rush University Medical Center, Chicago, IL, USA; [3]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

International Journal of Neuropsychopharmacology (2014), 17, 1507–1567. © CINP 2014. The online version of this article is published within an Open Access environment subject to the conditions of the Creative Commons Attribution licence http://creativecommons.org/licenses/by/3.0/
doi:10.1017/S1461145714000546

A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults

Roger S. McIntyre[1], Søren Lophaven[2] and Christina K. Olsen[2]

[1]Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto, Toronto, ON, Canada
[2]H. Lundbeck A/S, Copenhagen, Denmark

J Psychopharmacol. 2017 Mar;31(3):365-376. doi: 10.1177/0269881116667710. Epub 2016 Sep 28.

In vivo and in vitro effects of vortioxetine on molecules associated with neuroplasticity.

Kugathasan P[1], Waller J[1], Westrich L[1], Abdourahman A[1], Tamm JA[1], Pehrson AL[1], Dale E[1], Gulinello M[2], Sanchez C[1], Li Y[1].

Author information

Abstract

Neuroplasticity is fundamental for brain functions, abnormal changes of which are associated with mood disorders and cognitive impairment. Neuroplasticity can be affected by neuroactive medications and by aging. Vortioxetine, a multimodal antidepressant, has shown positive effects on cognitive functions in both pre-clinical and clinical studies. In rodent studies, vortioxetine increases glutamate neurotransmission, promotes dendritic branching and spine maturation, and elevates hippocampal expression of the activity-regulated cytoskeleton-associated protein (Arc/Arg3.1) at the transcript level. The present study aims to assess the effects of vortioxetine on several neuroplasticity-related molecules in different experimental systems. Chronic (1 month) vortioxetine increased Arc/Arg3.1 protein levels in the cortical synaptosomes of young and middle-aged mice. In young mice, this was accompanied by an increase in actin-depolymerizing factor (ADF)/cofilin serine 3 phosphorylation without altering the total ADF/cofilin protein level, and an increase in the GluA1 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor phosphorylation at serine 845 (S845) without altering serine 831 (S831) GluA1 phosphorylation nor the total GluA1 protein level. Similar effects were detected in cultured rat hippocampal neurons: Acute vortioxetine increased S845 GluA1 phosphorylation without changing S831 GluA1 phosphorylation or the total GluA1 protein level. These changes were accompanied by an increase in α subunit of Ca^{2+}/calmodulin-dependent kinase (CaMKIIα) phosphorylation (at threonine 286) without changing the total CaMKIIα protein level in cultured neurons. In addition, chronic (1 month) vortioxetine, but not fluoxetine, restored the age-associated reduction in Arc/Arg3.1 and c-Fos transcripts in the frontal cortex of middle-aged mice. Taken together, these results demonstrated that vortioxetine modulates molecular targets that are related to neuroplasticity.

Neuropharmacology. 2016 Apr;103:143-54. doi: 10.1016/j.neuropharm.2015.12.012. Epub 2015 Dec 15.

Vortioxetine promotes maturation of dendritic spines in vitro: A comparative study in hippocampal cultures.

Waller JA[1], Chen F[2], Sánchez C[3].

Author information

Abstract

Cognitive dysfunction is prevalent in patients with major depressive disorder (MDD), and cognitive impairments can persist after relief of depressive symptoms. The multimodal-acting antidepressant vortioxetine is an antagonist at 5-HT3, 5-HT7, and 5-HT1D receptors, a partial agonist at 5-HT1B receptors, an agonist at 5-HT1A receptors, and an inhibitor of the serotonin (5-HT) transporter (SERT) and has pro-cognitive properties. In preclinical studies, vortioxetine enhances long-term potentiation (LTP), a cellular correlate of neuroplasticity, and enhances memory in various cognitive tasks. However, the molecular mechanisms by which vortioxetine augments LTP and memory remain unknown. Dendritic spines are specialized, actin-rich microdomains on dendritic shafts and are major sites of most excitatory synapses. Since dendritic spine remodeling is implicated in synaptic plasticity and spine size dictates the strength of synaptic transmission, we assessed if vortioxetine, relative to other antidepressants including ketamine, duloxetine, and fluoxetine, plays a role in the maintenance of dendritic spine architecture in vitro. We show that vortioxetine, ketamine, and duloxetine induce spine enlargement. However, only vortioxetine treatment increased the number of spines in contact with presynaptic terminals. In contrast, fluoxetine had no effect on spine remodeling. These findings imply that the various 5-HT receptor mechanisms of vortioxetine may play a role in its effect on spine dynamics and in increasing the proportion of potentially functional synaptic contacts.

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KEYWORDS: Antidepressant; Multimodal; Neuroplasticity; Synapsin

PMID: 26702943 DOI: 10.1016/j.neuropharm.2015.12.012

[Indexed for MEDLINE]

Int J Neuropsychopharmacol. 2017 Oct 19. doi: 10.1093/ijnp/pyx070. [Epub ahead of print]

A network meta-analysis comparing effects of various antidepressant classes on the Digit Symbol substitution test (DSST) as a measure of cognitive dysfunction in patients with major depressive disorder.

Baune BT[1], Brignone M[2], Larsen KG[3].

⊕ Author information

Abstract

BACKGROUND: Major depressive disorder (MDD) is a common condition that often includes cognitive dysfunction. A systematic literature review of studies and a network meta-analysis (NMA) were carried out to assess the relative effect of antidepressants on cognitive dysfunction in MDD.

METHODS: MEDLINE ®, Embase ®, Cochrane, CDSR, PsychINFO ® databases, clinical trial registries, and relevant conference abstracts were searched for randomised controlled trials (RCTs) assessing the effects of antidepressants/placebo on cognition. An NMA comparing antidepressants was conducted using a random effects model.

RESULTS: The database search retrieved 11,337 citations of which 72 RCTs from 103 publications met the inclusion criteria. The review identified 86 cognitive tests assessing the effect of antidepressants on cognitive functioning. However, the Digit Symbol Substitution Test (DSST), which targets multiple domains of cognition and is recognised as being sensitive to change, was the only test that was used across 12 of the included RCTs and that allowed the construction of a stable network suitable for the NMA. The interventions assessed included selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and other non-SSRI/SNRIs. The NMA using the DSST showed that vortioxetine was the only antidepressant that improved cognitive dysfunction on the DSST versus placebo (standardised mean difference: 0.325 (95% CI=[0.120; 0.529], p=0.009). When comparing to other antidepressants, Vortioxetine was statistically more efficacious on the DSST versus escitalopram, nortriptyline, and the SSRI and TCA classes.

CONCLUSIONS: This study highlighted the large variability in measures used to assess cognitive functioning. The findings on the DSST indicate differential effects of various antidepressants on improving cognitive function in patients with MDD.

KEYWORDS: cognitive dysfunction; major depressive disorder; network meta-analysis; systematic literature review; vortioxetine

CLINICAL PHARMACOLOGY 1

Effect on Cardiac Repolarization

- The effect of vortioxetine 10 mg and 40 mg administered once daily on QTc interval was evaluated in a randomized, double-blind, placebo-, and active-controlled (moxifloxacin 400 mg), four-treatment-arm parallel study in **340 male subjects**. In the study the upper bound of the one-sided 95% confidence interval for the QTc was below 10 ms, the threshold for regulatory concern. The oral dose of 40 mg is sufficient to assess the effect of metabolic inhibition

Brintellix FDA Prescribing information, accessed on Feb 22 2016 at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf

CLINICAL PHARMACOLOGY 2

Pharmacokinetics

Vortioxetine pharmacological activity is due to the parent drug. The pharmacokinetics of vortioxetine (2.5 mg to 60 mg) are **linear** and dose-proportional when vortioxetine is administered once daily. The mean terminal half-life is approximately **66 hours**, and stead-state plasma concentrations are typically achieved within **two weeks** of dosing

Brintellix FDA Prescribing information, accessed on Feb 22 2016 at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf

CLINICAL PHARMACOLOGY 3

METABOLISM

Vortioxetine is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation. **CYP2D6** is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers.

Brintellix FDA Prescribing information, accessed on Feb 22 2016 at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf

CLINICAL PHARMACOLOGY 4

Interactions with Drugs that Interfere with Hemostasis

- Following coadministration of stable doses of warfarin (1 to 10 mg/day) with multiple daily doses of vortioxetine, no significant effects were observed in INR, prothrombin values or total warfarin (protein bound plus free drug) pharmacokinetics for both R- and S-warfarin
- Coadministration of aspirin 150 mg/day with multiple daily doses of Vortioxetine had no significant inhibitory effect on platelet aggregation or pharmacokinetics of aspirin and salicylic acid
- Patients receiving other drugs that interfere with hemostasis should be carefully monitored when vortioxetine is initiated or discontinued

Brintellix FDA Prescribing information, accessed on Feb 22 2016 at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf

PREGNANCY

Pregnancy Category C

- There are no adequate and well-controlled studies of Vortioxetine in pregnant women.
- Vortioxetine caused developmental delays when administered during pregnancy to rats and rabbits at doses 15 and 10 times the maximum recommended human dose (MRHD) of 20 mg, respectively. Developmental delays were also seen after birth in rats at doses 20 times the MRHD of vortioxetine given during pregnancy and through lactation. There were no teratogenic effects in rats or rabbits at doses up to 77 and 58 times, the MRHD of vortioxetine, respectively, given during organogenesis. The incidence of malformations in human pregnancies has not been established for vortioxetine.
- All human pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss.
- Vortioxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Brintellix FDA Prescribing information, accessed on Feb 22 2016 at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf

Vortioxetine is well tolerated

Vortioxetine (10 mg) does not exhibit many of the side effects typical of SSRIs and SNRIs:
(Vortioxetine SmPC)

Weight neutral

Low withdrawal rate and discontinuation symptoms

Sexual dysfunction at placebo level*

Sleep disturbance at placebo level

Mild to moderate transient nausea

Low rate of safety-related adverse events

Low rate of treatment emergent adverse events

Low potential for drug–drug interactions

*Vortioxetine 20 mg was associated with an increase in TESD relative to placebo

Vortioxetine. EU Summary of Product Characteristics. 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002717/WC500159449.pdf. Accessed October 2015.

Please refer to the SmPC/PI for further information about safety events

The safety and tolerability profile of vortioxetine is based on a large

The tolerability profile of vortioxetine was established in a robust programme of clinical trials including more than 3700 patients treated with vortioxetine in short-term (≤12 weeks) studies

- In clinical trials, the **most c**ommon adverse event was nausea
- Adverse events were usually mild or moderate, and occurred within the first two weeks of treatment
- The events were usually transient and did not generally lead to cessation of therapy
- Comparatively low withdrawal rate due to treatment-emergent adverse events with vortioxetine

Baldwin et al. J Psychopharmacol. 2016 Feb 9. pii: 0269881116628440. [Epub ahead of print]Vortioxetine. EU Summary of Product Characteristics. 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002717/WC500159449.pdf. Accessed October 2015; Baldwin DS et al. *Future Neurol*. 2015;10(2); 79–89.

Nausea was the most reported TEAE in 11 short-term clinical trials with vortioxetine

Table 3. TEAEs with an incidence of ≥5% in any group during the core treatment period (APTS) in 11 short-term MDD studies.

Preferred term	Placebo (*n*=1817)	VOR 5 mg (*n*=1013)	VOR 10 mg (*n*=894)	VOR 15 mg (*n*=449)	VOR 20 mg (*n*=662)	VLF 225 mg (*n*=113)	DUL 60 mg (*n*=753)
PYE	241.1	128.7	122.3	60.7	91.1	11.8	101.4
Patients with TEAEs	1052 (57.9%)	657 (64.9%)	546 (61.1%)	309 (68.8%)	433 (65.4%)	85 (75.2%)	571 (75.8%)
Nausea	148 (8.1%)	212 (**20.9**%)	208 (**23.3**%)	140 (**31.2**%)	184 (**27.8**%)	38 (**33.6**%)	257 (**34.1**%)
Headache	238 (13.1%)	144 (14.2%)	114 (12.8%)	66 (14.7%)	83 (12.5%)	32 (**28.3**%)	97 (12.9%)
Dry mouth	108 (5.9%)	71 (7.0%)	51 (5.7%)	27 (6.0%)	44 (6.6%)	19 (**16.8**%)	125 (**16.6**%)
Dizziness	101 (5.6%)	58 (5.7%)	48 (5.4%)	32 (7.1%)	42 (6.3%)	11 (9.7%)	92 (**12.2**%)
Diarrhoea	96 (5.3%)	71 (7.0%)	50 (5.6%)	42 (9.4%)	40 (6.0%)	5 (4.4%)	66 (8.8%)
Vomiting	20 (1.1%)	29 (2.9%)	37 (4.1%)	29 (**6.5**%)	30 (4.5%)	4 (3.5%)	31 (4.1%)
Constipation	56 (3.0%)	33 (3.3%)	34 (3.8%)	25 (5.6%)	28 (4.2%)	11 (**9.7**%)	73 (**9.7**%)
Insomnia[a]	73 (4.0%)	52 (5.1%)	33 (3.7%)	9 (2.0%)	22 (3.3%)	18 (**15.9**%)	61 (**8.1**%)
Somnolence	43 (2.4%)	31 (3.1%)	23 (2.6%)	12 (2.7%)	21 (3.2%)	1 (0.9%)	64 (**8.5**%)
Fatigue	51 (2.8%)	31 (3.1%)	25 (2.8%)	16 (3.6%)	16 (2.4%)	11 (**9.7**%)	60 (**8.0**%)
Decreased appetite	18 (1.0%)	20 (2.0%)	7 (0.8%)	3 (0.7%)	12 (1.8%)	1 (0.9%)	52 (**6.9**%)
Sexual dysfunction[b]	18 (1.0%)	16 (1.6%)	16 (1.8%)	7 (1.6%)	12 (1.8%)	14 (**12.4**%)	34 (4.5%)
Tremor	7 (0.4%)	12 (1.2%)	3 (0.3%)	6 (1.3%)	6 (0.9%)	6 (**5.3**%)	14 (1.9%)
Vision blurred	19 (1.0%)	7 (0.7%)	6 (0.7%)	9 (2.0%)	4 (0.6%)	6 (**5.3**%)	19 (2.5%)
Hyperhidrosis	32 (1.8%)	24 (2.4%)	21 (2.3%)	8 (1.8%)	3 (0.5%)	17 (**15.0**%)	55 (**7.3**%)

% values **in bold** are ≥5% and >2 × placebo.

Baldwin et al. 2016; Journal of Psychopharmacology 1-11

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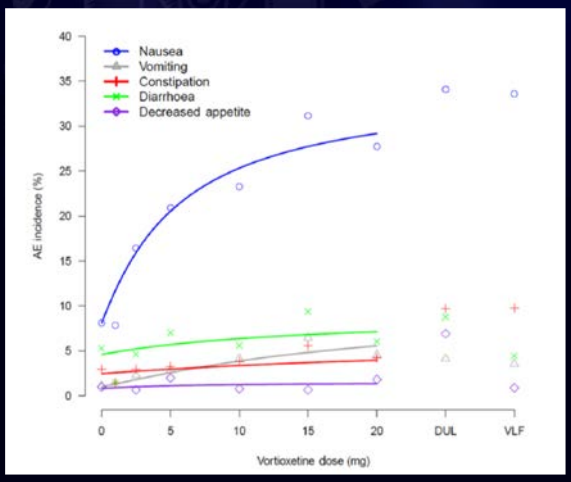
Nausea with Vortioxetine treatment was dose dependent



Baldwin et al. J Psychopharmacol. 2016 Feb 9. pii: 0269881116628440. [Epub ahead of print]

SIMILAR EFFECTS OF PBO ON BODY WEIGHT IN SHORT- AND LONG-TERM CLINICAL STUDIES[1]

Short-term treatment

- No clinically relevant weight changes, or differences between treatment groups[2–4]
  - Randomised, double-blind, placebo-controlled, active-referenced studies of vortioxetine (5, 10, 15 or 20 mg/day) in adults with depression
- In a study in elderly patients with depression, the changes in weight associated with vortioxetine were at placebo level[5]

Long-term treatment

- In the double-blind period of a relapse-prevention study in depression, the mean weight increase for vortioxetine (0.4 kg) was similar to placebo (0.6 kg)[6]

1. Baldwin et al. J Psychopharmacol. 2016 Feb 9. pii: 0269881116628440. [Epub ahead of print]; 2. Boulenger JP et al. *Int Clin Psychopharmacol* 2014;29:138–149; 3. Alvarez E et al. *Int J Neuropsychopharmacol* 2012;15,589–600; 4. Henigsberg N et al. *J Clin Psychiatry* 2012;73(7):953–959; 5. Katona C et al. *Int Clin Psychopharmacol* 2012;27:215–223; 6. European Medicines Agency CHMP. Brintellix (vortioxetine) EPAR. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002717/WC500159447.pdf Accessed October2015

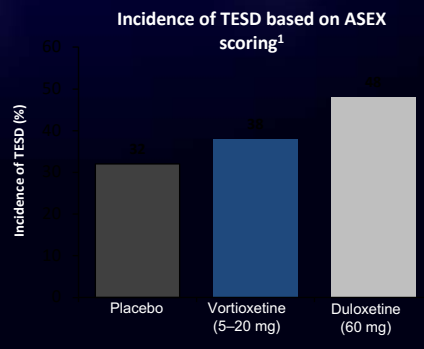
SEXUAL DYSFUNCTION DURING VORTIOXETINE TREATMENT WAS SIMILAR TO PLACEBO

Sexual dysfunction (TEAE reports)

- Sexual dysfunction during treatment with vortioxetine was low and similar to that in the placebo group (1.6 vs 0.9%)[1]

Sexual dysfunction (ASEX scale)

- No difference from placebo for vortioxetine 5–15 mg[2]
- Increase in TESD from 5 mg to 20 mg vortioxetine; no clear dose–response relationship[1]
- Vortioxetine 20 mg was associated with an increase in TESD (46%)[1]



Duloxetine was included as active reference for study validation, not for comparison of effect size

1. Baldwin et al. J Psychopharmacol. 2016 Feb 9. pii: 0269881116628440. [Epub ahead of print]http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002717/human_med_001714.jsp&mid=WC0b01ac058001d124. Accessed October 2015