ESCITALOPRAM IN THE TREATMENT OF ANXIETY AND PANIC ATTACKS

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Escitalopram has established itself as an effective medication in the treatment of anxiety and panic attacks, when combined in an integrated treatment program. This article provides a brief overview of the use of escitalopram in anxiety and panic disorder.

Keywords: escitalopram, selective serotonin reuptake inhibitor, SSRI, medication, depression, anxiety, panic disorder, treatment, psychiatry

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Introduction

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) used for the treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorder, panic attacks, obsessive-compulsive disorder, premenstrual dysphoric disorder and, more experimentally, in other conditions, either by itself or in combination. It has a reputation of usually being well tolerated which may be a result of its high receptor specificity.

Escitalopram exerts a highly selective, potent, and dose-dependent inhibitory effect on the serotonin transport system. This leads to changes of neurotransmitter levels, but also, with a longer delay of the receptor distributions at various locations. This change in receptor distributions is probably one reason why the anti-anxiety and antidepressant effect can take a couple of weeks to set in. By inhibiting the reuptake of serotonin into presynaptic nerve endings, it enhances the activity of serotonin in the central nervous system. Furthermore, aside from binding to an active site on a receptor, escitalopram can also influence the activity of a receptor by binding to allosteric sites.

Anxiety

Generalized anxiety disorder is characterized by an excessive and inappropriate worrying that is persistent and not restricted to particular circumstances. In this respect, anxiety is distinct from fear, which has a specific target. One may, for example, be afraid of a particular dangerous animal, while in anxiety there is uncertainty about the source of danger. This is why anxiety can be, and often is generalized.

Patients have physical anxiety symptoms, such as tachycardia and tremor, and key psychological symptoms, including restlessness, fatigue, difficulty in concentrating, irritability, and disturbed sleep. The 12-month prevalence is between two and three percent (being more common in old age), and the associated functional impairment is similar to that with major depression. However, many of those who might benefit from treatment are not recognized or treated, which is disappointing, as a broad range of evidence-based treatments is available. (Lader, 2015) The impairment of daily life can be substantial, up to the point where a patient is no longer able to leave the home, or even the bed.

Treatment

Treatment for anxiety is often primarily done with psychotherapy and several supportive therapies, such as mindfulness meditation and others, particularly if the impairments are not too great. However, many patients benefit considerably from medication, and in several cases it is strongly indicated, especially where impairment have made a normal everyday life impossible.

On the medication side, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and MAO inhibitors have all demonstrated their effectiveness in the treatment of panic disorder. However, the tricyclics are associated with potentially fatal arrhythmias and MAO inhibitors must be used with caution in many populations (Yamada and Yasuhara 2004).

The most common first-line approach is thus to use an SSRI, such as escitalopram, in combination with a stand-by benzodiazepine until the SSRI works. Escitalopram 10–20 mg/day is usually considered effective, safe, and well tolerated in the treatment of patients with generalized anxiety disorder, though specific cautions and contraindications need to be observed as in any medication. In clinical practice, many patients may have to take a dose of 15 mg or 20 mg to notice a clear effect against anxiety,

which, however, can often be reduced over time to a 10mg long-term maintenance dose.

Clinical data suggests that escitalopram treatment is very effective for panic disorder in terms of both response and remission rates and that long-term pharmacotherapy with escitalopram continuously improved panic symptoms and functional disability in Korean patients with panic disorder. (Choi et al., 2012)

Davidson and colleagues reported in a randomized double-blind study improvement in the Hamilton Rating Scale for Anxiety (HAM-A) score for the escitalopram-treated group as compared to the placebo-treated group beginning at Week 1 and at each study visit thereafter. Response rates at Week 8 were 68% for escitalopram and 41% for placebo for those who completed the study. Treatment with escitalopram was well tolerated, with low rates of reported adverse events and an incidence of discontinuation due to adverse events not statistically different from placebo. (Davidson, Bose, Korotzer, & Zheng, 2004) The data also reflects the common observation that anxiety can fluctuate and abate even without medication.

Escitalopram also appears to be beneficial for the treatment of sleep problems in patients with depression and generalized anxiety disorder. Using data from twenty-two randomized,

controlled trials, in patients with generalized anxiety disorder the subjective level of insomnia was significantly less in the escitalopram treatment group as compared to those on a placebo, although there was no difference to paroxetine or venlafaxine. (Stein & Lopez, 2011)

Interestingly, escitalopram facilitated the recognition of sadness and inhibited the recognition of happiness in male, but not female faces. Serotonin appears to modulate the recognition of emotional faces. (Alves-Neto, Guapo, Graeff, Deakin, & Del-Ben, 2010)

Panic Attacks

Panic disorder is characterized by recurrent panic attacks, persistent concerns about additional attacks, and worry about the implications of the attack or significant changes in behaviour related to the attacks. The panic attacks are unexpected and come with a feeling of imminent door or death, mostly a feared los of control over vital bodily functions. Particularly frequent are for example the fear of a heart attack or not being able to breath anymore. As patients often feel even less in control when among people or in open spaces, agoraphobia frequently develops when the panic attacks remain untreated. As mentioned, psychotherapy is particularly helpful over the long-term, while medication can be effective within a few weeks (regular antidepressant medication) or even within 45 minutes (stand-by benzodiazepines).

Panic attacks are rapidly escalating occurrence of multiple physical and psychological symptoms of intense distress. Epidemiological surveys have shown lifetime prevalence of panic disorder at around 5%, while the onset is usually in early adulthood, and females may be in the majority. Panic disorder is

highly comorbid with other anxiety disorders, such as social anxiety disorder, generalized anxiety disorder, major depressive disorder, and substance use disorders.

Causes

The pathogenesis of panic disorder is complex, likely involving psychological, biological, and survival-related evolutionary factors and their interactions. How an individual communicates with oneself and with others, the social context, seems to play a significant role (Haverkampf, 2017b, 2017a). While numerous interacting neuroanatomical sites have been implicated in the pathogenesis of panic attacks, a dysfunction of the serotonin system appears to play a crucial role in development and perpetuation of panic attacks (Grove 1997; Maron 2006).

On a biological level, panic attacks originate from a dysfunction in the brain fear network that integrates various structures of the brainstem, the amygdala, the hypothalamus, and the cortical regions. (Maron, Hettema, & Shlik, 2010) An abnormal sensitivity in the brain mechanisms of fear and alarm response involving a network of neuronal pathways and multiple neurotransmitter systems, including serotonin, norepinephrine, GABA, and others may play a role.

In a randomized, double-blind, placebo-controlled, 10-week trial with 366 adults with panic disorder, 128 were assigned to escitalopram at 10 to 20 mg daily. Escitalopram was more effective than placebo in reducing both anticipatory anxiety and the frequency and intensity of panic attacks, and on the Panic and Agoraphobia scale, escitalopram showed significant improvement from week four onwards. (Stahl, Gergel, & Li, 2003) Escitalopram was not discontinued due to adverse effects at a higher level than placebo.

Chemistry

Racemic citalopram, an SSRI widely used in patients with major depressive disorder, possesses both an active S-enantiomer and clinically inactive R-enantiomer, two different non-superimposable mirror image forms of the same molecule. In animal models, R-citalopram has appeared to counteract the antidepressant effect, so that citalopram may be less effective than its S-enantiomer. The S enantiomer has high affinity for the serotonin transporter which is twice as high as citalopram's and 30 to 40 times higher than R-citalopram

R-citalopram seems to have a significant affinity only for the allosteric site of the transporter, which regulates the affinity of the ligand for the active site at the origin of serotonin reuptake inhibition (Jacquot, David, Gardier, & Sánchez, 2007). Unlike citalopram, escitalopram's pharmacologic action is not blocked by R-citalopram explaining its greater therapeutic efficacy and more rapid mode of action.

Escitalopram, on the other hand, is only the active S-enantiomer. In vitro and in vivo studies have shown that it inhibits the

serotonin transporter protein more potently than citalopram. For example, in vivo electrophysiological data indicated that escitalopram was four times more potent than citalopram in reducing the firing activity of presumed serotonergic neurons in the dorsal raphe nucleus of rat brain.

The Serotonin Transporter (SERT)

Escitalopram selectively binds to the human serotonin transporter (SERT). This activity inhibits serotonin reuptake and increases the amount of serotonin in synaptic clefts, which results in antidepressant action. Escitalopram has a highly selective, dose-dependent, inhibitory effect on SERT.

Genetic markers in the serotonin transporter are associated with panic disorder. (Gyawali et al., 2010) Studies have shown that changes in serotonin transporter metabolism appear to be associated with many different phenomena, including depression, OCD and generalized social phobia. The serotonin transporter is also present in platelets, where serotonin functions as a vasoconstrictive agent.

The serotonin transporter promoter haplotype is associated with variability in SSRI efficacy for late-life generalized anxiety disorder. The variability may result from a genetic effect on anxiety symptom variability unrelated to treatment, rather than a pharmacodynamic effect that has been previously assumed.

Further research is needed to understand the pharmacogenetic mechanism of this haplotype. (Lenze et al., 2010)

Pharmacokinetics

While the plasma half-life of escitalopram is about 30 hours, the half-life of its receptor occupancy has been estimated at 130 hours, a considerable length of time. This also means that the serotonin discontinuation syndrome in the case of escitalopram may be not as pronounced as that of some other SSRIs. An allosteric action could explain this prolonged occupancy.

Escitalopram is metabolized in the liver, mainly by CYP2C19, but also by CYP3A4 and CYP2D6. Escitalopram inhibits primarily only CYP2D6, leading to a favourable interactions profile with other drugs.

Clinical Efficacy

In a study on generalized anxiety by Davidson and colleagues, those completing 24 weeks of treatment, 92% responded, while using the last observation carried forward (LOCF), 75.9% responded. (Davidson, Bose, & Wang, 2005) In a study on social anxiety, escitalopram was effective in both younger and older patients, in male and female patients, and in patients with more and less severe social anxiety symptoms. (Stein, Kasper, Andersen, Nil, & Lader, 2004) Older adults with generalized anxiety disorder also seem to have a higher response rate for improvement than placebo, while in a study by Lenze and colleagues, response rates were not significantly different using an intention-to-treat analysis. (Lenze et al., 2009)

Psychological factors, however, can play a significant role in the effectiveness of an antidepressant. Faria and colleagues tested how expectancies influence SSRI efficacy in social anxiety disorder using truthful or deceiving verbal instructions. The number of responders was more than three times higher after open administration of escitalopram 20 mg compared to covert administration of the drug presented as “active placebo” in a cover story. (Faria et al., 2017)

Side Effects

Any medication can have side effects, and one needs to keep up to date on those. Escitalopram is generally regarded as well tolerated. In a study by Davidson and colleagues, results supported the long-term tolerability and effectiveness of escitalopram in the treatment of generalized anxiety disorder. Mean increase in weight from baseline was 3 lb. In the study, no clinically notable changes in mean laboratory, vital sign, or electrocardiographic values were observed. (Davidson et al., 2005)

Escitalopram seems superior compared with paroxetine, which has a less favourable tolerability profile. (Sanchez, Reines, & Montgomery, 2014) Paroxetine is associated with cholinergic muscarinic antagonism and potent inhibition of CYP2D6, and sertraline has moderate drug interaction issues in comparison with escitalopram. (Sanchez, Reines, & Montgomery, 2014) The favourable side effect profile of escitalopram may be associated with the fact that it is an allosteric serotonin reuptake inhibitor that is somewhat different from classical SSRIs.

Discontinuation symptoms

Discontinuation symptoms typically occur at the end of treatment with antidepressant drugs. One study compared discontinuation symptoms in patients with major depression during the post-therapy observation period after 27 weeks of therapy with escitalopram (20 mg/day) or paroxetine (40 mg/day). The escitalopram group exhibited less frequent discontinuation symptoms compared to the paroxetine group.

In another study, the incidence of discontinuation symptoms with escitalopram during tapered withdrawal was low; the symptoms primarily being dizziness (10–12%), nervousness (2–6%), and insomnia (2–6%). (Allgulander, Florea, & Huusom, 2006) The study also showed that escitalopram 20 mg/d significantly reduced the risk of relapse and was well tolerated in patients with generalized anxiety disorder.

Suicidality

In a study by Pedersen, there was no indication that escitalopram provoked suicidal behaviour compared to placebo in either major depression or anxiety disorders. Escitalopram was more efficacious versus placebo in lowering suicidal thoughts from weeks one through eight in the treatment of patients with major depressive disorder. (Pedersen, 2005) Still, caution should be exercised.

QT prolongation

Lengthening of the QT interval has been reported in escitalopram. One should be especially cautious in case of elderly patients, patients with liver dysfunction, defective CYP2C19 activity, or those that receive other drugs with an associated risk of QT prolongation.

Disclosure

The author reports no conflicts of interest in this work.

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References

Allgulander, C., Florea, I., & Huusom, A. K. T. (2006). Prevention of relapse in generalized anxiety disorder by escitalopram treatment. *The International Journal of Neuropsychopharmacology*, *9*(05), 495. https://doi.org/10.1017/S1461145705005973

Alves-Neto, W. C., Guapo, V. G., Graeff, F. G., Deakin, J. F. W., & Del-Ben, C. M. (2010). Effect of escitalopram on the processing of emotional faces. *Brazilian Journal of Medical and Biological Research*, *43*(3), 285–289. https://doi.org/10.1590/S0100-879X2010005000007

Choi, K.-W., Woo, J.-M., Kim, Y.-R., Lee, S.-H., Lee, S.-Y., Kim, E.-J., … Yu, B.-H. (2012). Long-term Escitalopram Treatment in Korean Patients with Panic Disorder: A Prospective, Naturalistic, Open-label, Multicenter Trial. *Clinical Psychopharmacology and Neuroscience : The Official Scientific Journal of the Korean College of Neuropsychopharmacology*, *10*(1), 44–48. https://doi.org/10.9758/cpn.2012.10.1.44

Davidson, J. R. T., Bose, A., Korotzer, A., & Zheng, H. (2004). Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study. *Depression and Anxiety*, *19*(4), 234–240. https://doi.org/10.1002/da.10146

Davidson, J. R. T., Bose, A., & Wang, Q. (2005). Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder. *The Journal of Clinical Psychiatry*, *66*(11), 1441–1446.

Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16420082

Faria, V., Gingnell, M., Hoppe, J. M., Hjorth, O., Alaie, I., Frick, A., … Månsson, K. N. T. (2017). Do you believe it? Verbal suggestions influence the clinical and neural effects of escitalopram in social anxiety disorder: a randomized trial. *EBioMedicine*, *24*, 179–188.

Gyawali, S., Subaran, R., Weissman, M. M., Hershkowitz, D., McKenna, M. C., Talati, A., … Glatt, C. E. (2010). Association of a Polyadenylation Polymorphism in the Serotonin Transporter and Panic Disorder. *Biological Psychiatry*, *67*(4), 331–338. https://doi.org/10.1016/J.BIOPSYCH.2009.10.015

Haverkampf, C. J. (2017a). *Anxiety and Panic Attacks (4)*. Retrieved from http://www.jonathanhaverkampf.com

Haverkampf, C. J. (2017b). *Communication-Focused Therapy (CFT)* (2nd ed.). Dublin: Psychiatry Psychotherapy Communication Publishing Ltd.

Jacquot, C., David, D. J., Gardier, A. M., & Sánchez, C. (2007). [Escitalopram and citalopram: the unexpected role of the R-enantiomer]. *L'Encephale*, *33*(2), 179–187. https://doi.org/10.1016/S0013-7006(07)91548-1

Lader, M. (2015). Generalized anxiety disorder. *Encyclopedia of Psychopharmacology*, 699–702.

Lenze, E. J., Goate, A. M., Nowotny, P., Dixon, D., Shi, P., Bies, R. R., … Pollock, B. G. (2010). Relation of serotonin transporter genetic variation to efficacy of escitalopram for generalized anxiety disorder in older adults. *Journal of Clinical Psychopharmacology*, *30*(6), 672–677. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21105279

Lenze, E. J., Rollman, B. L., Shear, M. K., Dew, M. A., Pollock, B. G.,

Ciliberti, C., … Reynolds, C. F. (2009). Escitalopram for Older Adults With Generalized Anxiety Disorder. *JAMA*, *301*(3), 295. https://doi.org/10.1001/jama.2008.977

Maron, E., Hettema, J. M., & Shlik, J. (2010). Advances in molecular genetics of panic disorder. *Molecular Psychiatry*, *15*(7), 681–701. https://doi.org/10.1038/mp.2009.145

Pedersen, A. G. (2005). Escitalopram and suicidality in adult depression and anxiety. *International Clinical Psychopharmacology*, *20*(3), 139–143.

Sanchez, C., Reines, E. H., & Montgomery, S. A. (2014). A comparative review of escitalopram, paroxetine, and sertraline: Are they all alike? *International Clinical Psychopharmacology*, *29*(4), 185–196. https://doi.org/10.1097/YIC.0000000000000023

Stahl, S. M., Gergel, I., & Li, D. (2003). Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *The Journal of Clinical Psychiatry*, *64*(11), 1322–1327. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14658946

Stein, D. J., Kasper, S., Andersen, E. W., Nil, R., & Lader, M. (2004). Escitalopram in the treatment of social anxiety disorder: Analysis of efficacy for different clinical subgroups and symptom dimensions. *Depression and Anxiety*, *20*(4), 175–181. https://doi.org/10.1002/da.20043

Stein, D. J., & Lopez, A. G. (2011). Effects of escitalopram on sleep problems in patients with major depression or generalized anxiety disorder. *Advances in Therapy*, *28*(11), 1021–1037. https://doi.org/10.1007/s12325-011-0071-8