Mirtazapine for treatment of visual snow syndrome: A case series with insights into pathophysiology and therapy

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Abstract
Background: Patients with visual snow syndrome (VSS) describe tiny flickering dots in the entire visual field resembling the noise of a poorly adjusted channel of analogue television with additional symptoms. Little is known about the pathophysiology and therapeutic options for this debilitating condition. Objectives: We present a case series of three patients with VSS taking mirtazapine, one of the most often prescribed antidepressants, and discuss the utility of antidepressants by reviewing our current understanding of pathophysiology and therapy. Results: Mirtazapine has no effect on VSS, neither positive nor negative. This is in line with the reports from the literature suggested only some beneficial effects from lamotrigine. Conclusions: Since the pathophysiology of VSS is not fully understood, we still rely on the reports of individual cases or patient series. This includes not only the positive, but also the negative results to avoid unnecessary treatment trials. Looking into the literature, antidepressants do not seem to be a solution for the visual symptoms. So far, best data exists for the anticonvulsant lamotrigine.

Keywords
Visual snow, visual snow syndrome, visual aura, pathophysiology, treatment, therapy, medication, antidepressants, mirtazapine, lamotrigine

Introduction
The main symptom of visual snow syndrome (VSS) is visual snow (VS), which patients describe as tiny flickering dots in the entire visual field resembling the noise of a poorly adjusted channel of analogue television, that is, TV-static. Patients have additional visual symptoms (Table 1) including palinopsia (afterimages), enhanced entoptic phenomena, such as floaters or blue field phenomenon, persistent photophobia, and impaired night-vision (nyctalopia). After the first publication of clinical criteria for VSS in 2014,² both interest in and understanding of the disease are steadily growing. Still little is known about the pathophysiology and therapeutic options for this debilitating condition.

So far, the etiology of VSS is not fully understood. In the vast majority of patients, no structural cause could be found in the ophthalmological and neurological examination and the encephalographic paraclinical tests, visual evoked potentials, and brain imaging or standard laboratory.³⁻⁶ However, occasionally, secondary causes can be identified, such as Creutzfeldt–Jakob disease or stiff-person syndrome.⁷,⁸

Although VSS is of benign character in respect of visual acuity and visual field, the impact on patients’ live can be disastrous. Until now, most publications on VSS treatment options are case reports or case series with only one retrospective cohort study.⁹

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In a previous study of 78 patients, 68 (87%) had a history of headache with 48 fulfilling migraine criteria (62%). Eleven (14%) had symptoms of depression according to a Patient Health Questionnaire (PHQ)-8 above 10 points.\(^2\) In a retrospective analysis of 58 patients, lifetime depression occurred in 41%, comorbid migraine in 52%.\(^9\) One therefore might expect that antidepressants would have some effect on VSS.

Here, we present case report of three patients with VSS taking mirtazapine, one of the most often prescribed antidepressants.\(^10\) Mirtazapine has so far not been mentioned for VSS, and we will discuss its utility in the context of current opinions on pathophysiology and therapy.

### Cases

All three patients had already started mirtazapine prior to presenting to our study for depression or sleep disturbance. Although depression was officially diagnosed only in two, all had a history of depression and were still showing symptoms. As part of our clinical routine, all patients are asked about their current and previous medication for VSS and other indication. If the patient stated a positive effect on VSS, we asked in more detail which symptoms had improved. In addition, we assess whether the symptoms of the main indication improved; for depression, we use PHQ-8 for quantification with a score greater than 10 indicating major depression.\(^11\)

**Case 1** was a 28-year-old female suffering from VSS for 2 years and comorbid migraine with aura since puberty. Besides VS, the patient described floaters, photophobia, tinnitus, loss of concentration, and irritability. The second most disturbing after VS was her increased sensitivity to light in all environments, especially to artificial lights. Mirtazapine was taken up to 30 mg, at presentation with 15 mg for 2 years for sleeping problems. The sleep improved, but there was no effect on VSS. The patient also suffered from a depressive syndrome with a PHQ-8 of 20 points although this was not officially diagnosed. There was no additional medication or any pharmaceutical trial before.

**Case 2** was a 22-year-old female suffering from VSS for 6 years. She did not have migraine. Besides VS, the patient described floaters, bright flashes, blue field entoptic phenomena with little cells and swirls, nyctalopia, photophobia, tinnitus, and irritability as well as lethargy. After VS, the patient ranked tinnitus as the second most disturbing symptom. She additionally had a diagnosis of depression for 2 years and started taking mirtazapine 30 mg 4 months ago, without an impact on mood but improved sleep. The patient still had a PHQ-8 of 15 points. There was an additional pharmaceutical trial before with St. John’s wort showing no effect on VSS. There was no other concomitant medication.

**Case 3** was a 34-year-old male suffering from VSS for 19 years. There was no history of migraine. Besides VS, the patient described palinopsia, floaters, nyctalopia, photophobia, tinnitus, loss of concentration, and irritability as well as lethargy. Additionally, the patient had the feeling of derealization, which he ranked as disturbing as VS itself. He took mirtazapine 30 mg for 8 years because of an initial depressed mood, showing an impact on mood and acceptance but not on VSS. At presentation, the patient did not suffer from depression as reflected in a PHQ-8 of 9 points. The patient stated that alcohol consumption could worsen VSS in intensity. There was no other concomitant medication.

### Discussion

In our case series, mirtazapine was not helpful for the treatment of VSS. As long as we have not fully understood the pathophysiology of VSS, we will depend mainly on reports of case series or individual reports, including not only positive but also negative results.

Mirtazapine has a dual mechanism that affects both adrenergic \(\alpha_2\)-receptors (auto- and hetero) and serotonergic receptors (5-HT\(_2\) and 5HT\(_3\)) resulting in a release of noradrenaline and serotonin. This is also the explanation for its successful use in depression, being its main but not only clinical indication besides anxiety and sleeping disorders. The latter one is mainly distributed by its potent activity as a strong inverse agonist of the histamine H\(_1\) receptor.\(^12,\(^13\)\) The transmitters involved in VSS are so far unknown, but our data suggest that noradrenaline and serotonin might not be of particular relevance.

When it is not noradrenaline or serotonin, what could then be the mechanism behind VSS? There is still no straight answer, but we will briefly discuss here the current understanding of pathophysiology and treatment options of this condition.

### Pathophysiology

The key feature of VSS is its stereotypic presentation that underscores that it is a unique clinical condition.\(^2,\(^14,\(^15\)\) Its main symptom, VS, that is, persistent visual noise, is not limited to a specific part of the visual field and clearly does not follow retinotopy. It rather covers the entire visual field,
making it less possible to be caused by migraine aura.\textsuperscript{2,14,16} More likely, the origin should be located somewhere at or behind the lateral geniculate nucleus when visual information merges from both eyes for the first time.\textsuperscript{15,17,18} However, the focus in interpreting VSS should not be solely on the static but also on the syndrome-defining accompanying symptoms like palinopsia, enhanced entoptic phenomena, and photophobia that might better be explained by a more general visual processing deficit than just by a structural one.\textsuperscript{2,5,18}

A dysfunction of higher order visual processing comes from the first functional neuroimaging study using fluorodeoxyglucose–positron emission tomography (\textsuperscript{18}F-FDG–PET) in 17 VS patients and 17 controls showing hypermetabolism in the right lingual gyrus.\textsuperscript{19} Electro-physical studies using visual evoked potentials showed significantly prolonged N145 latency in 18 patients with VSS pointing to the visual association cortex,\textsuperscript{18} with normal P100 latency and amplitude reflecting a normal functioning visual pathway anterior to the primary visual cortex. However, there is also conflicting data suggesting rather involvement of the primary visual cortex than the association cortex due to loss of habituation of repetitive visual evoked potentials, lowered phosphate thresholds, reduction in gamma-band power, and a dysfunction in visual tasks specific for the primary visual cortex but not for the association cortex.\textsuperscript{20–23} Additionally, there is a more global thinking of VS being a disorder of sensory processing which might explain the involvement of other modalities, such as hearing with highly comorbid tinnitus; or a more localized theory of thalamocortical dysrhythmia based on an imbalance between the konio- and magnocellular pathway.\textsuperscript{17} This disturbance further could be sustained by a cortical trigger, for example, the discussed cortical hyperexcitability.\textsuperscript{17,23}

Worth to discuss is the model of stochastic resonance considered by Metzler et al. using the whole VSS in all its facets, that is, combining common visual and nonvisual symptoms.\textsuperscript{1,17,19,25} Briefly, it is based upon the knowledge that the addition of just a little noise sharpens the sensory system to better detect low-threshold content, even between various sensory inputs. Accordingly, this would explain the involvement of other sensory disturbances, such as photophobia, tinnitus or entoptic phenomena.\textsuperscript{25} Importantly, the suffering from each of these can exceed the suffering from VS itself. Photophobia, for instance, reaches the levels in VSS comparable to those of chronic migrainers during attacks but is present on a continuous basis.\textsuperscript{26}

VSS seems to be tenacious to treat. However, some of the accompanying visual or nonvisual symptoms might be better accessible for treatment.

**Treatment**

So far, there is no reliable treatment for VSS, and to the best of our knowledge, we derive conclusions from small case series and experience with migraine aura. Our limited understanding of the pathophysiology of VSS hinders the conduction of targeted randomized trials. Further, VSS just gets newly recognized as an entity on its own, with a growing interest not only what could be done in the future but also what has been done unknowingly in the past. Following this question, the first data from a retrospective cohort analysis came from van Dongen et al. who described a cohort of 58 patients with VSS. Of these, 29 were treated.\textsuperscript{9} The medication most often tried was lamotrigine being partially effective in 5 of 26 without a complete remission, followed by topiramate (partially effective in 1 of 4). Ineffective were valproate in seven patients, acetazolamide in two patients, and flunarizine in one patient. In one case report, a complete remission was described for valproate.\textsuperscript{27} Another patient improved by taking lamotrigine. The authors speculate that this effect might be due to the normalization of an initially decreased habituation of repetitive visual evoked potentials, but an effect of comorbid migraine cannot be ruled out.\textsuperscript{20} Other occasional effective treatments in case reports were baclofen, naproxen, propranolol, sertraline, and verapamil.\textsuperscript{2,19,28,29}

Some patients with VSS do not try pharmacological treatment as also reflected in the retrospective cohort study from van Dongen et al.\textsuperscript{9} This might be due to the lack of understanding of the mechanism of VSS resulting in potential concerns about the possible worsening of the symptoms. So far, only amitriptyline and topiramate have reportedly been associated with worsening VSS.\textsuperscript{19} Lauschke et al. offered a non-pharmaceutical approach by using tinted lenses mostly in the blue–yellow spectrum that gave 11 of the 12 patients relief and supports the theory of thalamocortical dysrhythmia.\textsuperscript{17}

It is interesting that there are nearly no reports on the use of antidepressants for VSS, considering the impact of VSS on mood and anxiety. That is even more remarkable in the context of mirtazapine being one of the most frequently described antidepressants in Germany in the last years.\textsuperscript{10} As patients with VSS are often misinterpreted within the framework of psychogenic disorders, the number should be even higher. One potential explanation could be that mirtazapine was indeed used, but without effect, and thus has not been judged worth reporting.

**Limitations**

One limitation is that VSS has not been assessed prior to starting treatment with mirtazapine, as the medication was already taken before presenting to us for the first time. Therefore, some slight improvement might have been overseen. Additionally, we depended more on subjective impression than on objective data as there is so far no clinical tool to assess VSS symptoms as regards quantity or quality. Another point is that mirtazapine was taken only up to 30 mg/day, thus we cannot rule out that higher doses could be helpful as it is known that mirtazapine shows a dose-dependent effects, where at higher plasma levels the
antihistaminic effect decreases while the noradrenergic effect increases.\textsuperscript{12}

**Conclusion**

VSS keeps it secrets, and there is still no ideal medical approach. The best data exist for lamotrigine, which therefore could be discussed off-label with patients. Despite VSS having high impact on patients’ mood, antidepressants do not seem to be a solution for the visual symptoms. VSS deserves more attention, and we encourage physicians to not only present medications helpful but also the ones being unsuccessful to avoid unnecessary trials in other patients.

**Author contributions**

OE was involved in acquisition, conception, analysis and interpretation of data and also helped writing manuscript. CJS helped in acquisition, analysis, and interpretation of data and in revising the manuscript. All authors approved the final version of the manuscript.

**Availability of data and materials**

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Declaration of conflicting interests**

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: OE has received honoraria for consulting within the past 3 years from Novartis Pharma and CJS has received travel grants, honoraria for advisory boards, consulting, and as a speaker, within the past 3 years, from Novartis, Eli Lilly, TEVA Pharmaceuticals, Allergan, Almirall, Amgen, MindMed, and Grünenthal.

**Ethical approval**

This case series is a part of a larger study on visual snow syndrome that was approved by the ethics committee of the Ludwig Maximilians University Munich (227-15). All patients gave written informed consent.

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