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Functional Somatic Symptoms in Children and Adolescents: The Stress-System Approach to Assessment and Treatment

Kasia Kozłowska, Stephen Scher, and Helene Helgeland

Online Supplement 5.1

Pharmacological Interventions to Improve Sleep in Children with Functional Somatic Symptoms

In this supplement to Chapter 5, we summarize the pharmacological interventions that we have found useful over the last decade to help stabilize sleep in children when simple interventions have proved ineffective.

As discussed in Chapter 5, in the first author's (KK's) Mind-Body Program – which includes a specialist pharmacist who works in the Psychological Medicine Department – we sometimes use medications to stabilize sleep in children who are admitted to the program for the treatment of functional somatic symptoms. Our consistent experience in the Mind-Body Program has been that behavioural interventions \pm melatonin are not always sufficient to stabilize our patients' sleep and to facilitate the body's own nighttime restorative functions – the essential first step in successful treatment. We therefore use medication, when needed, in a judicious, time-limited manner. We believe that stabilization of sleep contributes to our excellent outcome data, which shows that less than a sixth of our patients go on to experience chronic ill health such as a chronic functional disorder,

chronic anxiety or depression, or other long-term mental health disorder (see Online Supplement 2.1).

In the broader literature there is a lot of discussion pertaining to the use of medications for stabilizing sleep, because of concerns pertaining to the potential for adverse side effects and long-term misuse by patients (Nagy 2016; Brett 2015). The complicated process of assessing risk – the risk of utilizing a medication and causing potential harm (in this case, medication side effects) versus the risk of not utilizing a medication and causing potential harm (in this case, illness chronicity) – is the bread and butter of clinical work and part of day-to-day clinical decision making when working with children who are very ill and who are very disabled by their functional somatic symptoms. We see no evidence that our judicious use of medication for sleep stabilization has been a source of harm. That said, we use small doses for limited time periods, and we monitor the children very carefully.

The importance of the sleep intervention is underscored by some recent research that actually links sleep disturbance and functional impairment in adults with functional neurological disorder (FND) (Graham and Kyle 2017). There is also an increasing evidence base for using medication as a neuromodulator in chronic pain and a range of functional somatic symptoms seen in adults with disorders of gut-brain interactions (Tornblom and Drossman 2018).

In this context we summarize below the pharmacological interventions that we have found useful over the last decade to help stabilize sleep in children when simple interventions have proved ineffective. The material reflects our clinical experience as shaped by the ever-increasing knowledge about sleep-wake circuitry (see, e.g., Schwartz and Gozian [2013]) and about the neurobiology of our patient groups (see summary in Kozłowska [2017]), along with the evidence available in the current literature about off-label applications of potentially useful medications (see references cited throughout this supplement and in Chapter 5).

- *Melatonin* 3–9 mg immediate-release preparation, if sleep initiation is the problem. The 3 mg dose is always trialled first. The melatonin can be combined with any of the medications below. Melatonin, a hormone produced by the pineal gland at bedtime, regulates sleep

and wakefulness. For mechanisms of action and rationale, see Schwartz & Goradia (2013).

- *Melatonin* 2–8 mg slow-release preparation, if sleep maintenance is the problem. The 2 mg dose is always trialled first. The melatonin can be combined with any of the medications below.
- *Clonidine* 0.025 mg (i.e., quarter of 0.1 mg tablet) to 0.1 mg (depending on child's weight) at bedtime can be especially helpful if the child has a very high level of arousal at night or if she experiences trauma-related nightmares or flashbacks associated with poor sleep. Clonidine, an alpha-2 agonist, has an inhibitory action primarily at the adrenergic alpha-2 autoreceptor of the locus coeruleus, which gives rise to a massive noradrenaline-containing projection throughout the brain, including the amygdala. Clonidine is effective in controlling hyper-arousal, hypervigilance, sleep disruption, exaggerated startle responses, and nightmares in war veterans with PTSD and in maltreated children (Strawn and Geraciotti 2008; Belkin and Schwartz 2015; Perry 1994). Patients with functional somatic symptoms (e.g., chronic pain and FND) also show activation of the amygdala (Simons et al. 2014; Voon et al. 2010), increased autonomic arousal (down-regulation in parasympathetic function and up-regulation of sympathetic function, and increased cortical arousal) (see Chapters 6 and 11).

Clonidine is also helpful in managing symptoms of opiate withdrawal. Although opiates alleviate pain in the short term, using them to alleviate chronic pain ends up potentiating the pain (Grace et al. 2016; Trang et al. 2015).

Clonidine can be combined with melatonin. It can also be combined with melatonin and a small dose of quetiapine. There are no concerns pertaining to tolerance or addiction. The therapeutic effect lasts approximately four hours. For mechanisms of action and rationale, see Schwartz and Goradia (2013), Belkin and Schwartz (2015), and Naguy (2016).

- *Quetiapine* 6.25–37.5 mg is an atypical antipsychotic registered for the treatment of bipolar disorder, schizophrenia, treatment-resistant

depression, and generalized anxiety disorder. Quetiapine is sedating, dampens cortical arousal, and promotes sleep and normalization of sleep architecture via a complex combination of mechanisms (Schwartz and Goradia 2013). An accumulating evidence base supports the use of quetiapine as a neuromodulator in chronic pain conditions and as a useful medication for stabilizing sleep in patients with chronic pain or with other functional somatic symptoms seen in disorders of gut-brain interactions (see Tornblom and Drossman [2018] for a review of studies). In addition, most patients with functional somatic symptoms (in addition to the just-mentioned presentations requiring larger doses) can be helped with very small doses of quetiapine (6.25–37.5 mg total, per day). Because of its potential for weight gain and metabolic side effects, we use quetiapine as an interim measure (usually up to three months). Once sleep has stabilized and the child's function has improved, there is usually no problem withdrawing the quetiapine. Quetiapine can be combined with melatonin or clonidine.

- *Fluvoxamine* (usual dose of 25 mg morning and 50 mg at night) can be used if an SSRI is indicated, as when the disturbed sleep is a consequence of anxiety or depression. Fluvoxamine is the most sedating of the SSRIs. Fluvoxamine can be combined with melatonin, clonidine, or quetiapine.
- *Mirtazapine* 5–45 mg, depending upon the size and age of patient and presence or absence of depression, is a tetracyclic antidepressant with sedating properties. A growing evidence base supports the use of mirtazapine as a neuromodulator in adult patients with somatic symptoms associated with disorders of gut-brain interactions (Tornblom and Drossman 2018), particularly in the presence of comorbid anxiety or depression. Because of its sedating properties – histamine-1 receptor antagonism – it can be useful in stabilizing sleep (Schwartz and Goradia 2013). Weight gain is a potential problem. Mirtazapine can be combined with melatonin and clonidine.
- *Promethazine* – a phenothiazine – is another alternative that is used by some clinicians. Its sedating (and weight-gain) properties are also

associated with histamine-1 receptor antagonism. We have used it infrequently in the Mind-Body Program. Dosing would start at 5–10 mg (i.e., half to one 10 mg tablet), with a potential increase to 25 mg in adult-sized adolescents.

- *Tricyclic antidepressants* are another alternative that is used by some clinicians for sleep management in the presence of chronic pain (Tornblom and Drossman 2018). We rarely use tricyclics, because they have often been tried before the child is referred to us and because they interact with SSRIs, which we use if the child has significant comorbid anxiety or depression.

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