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SOCIAL ANXIETY DISORDER: EPIDEMIOLOGY, BIOLOGY AND TREATMENT

SOZIALPHOBIE: EPIDEMIOLOGIE, BIOLOGIE UND THERAPIE

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SUMMARY

Social anxiety disorder (SAD) is considered to be one of the most common anxiety disorders. Despite its high prevalence, the disorder is still considerably underdiagnosed and undertreated. SAD shows a typically early onset in childhood or early adolescence and generally becomes chronic. The disease places a massive burden on patients lives, affecting not only their social interactions but also their educational and professional activities, thereby constituting a severe disability. Although substantial progress in the study of the etiology of SAD has been made, no commonly accepted model has emerged yet. Data from genetic and neuroimaging studies point towards a contribution of several neurotransmitter systems (i.e. norepinephrine, dopamine and serotonin) to the pathophysiology of this disorder. Functional magnetic resonance imaging studies have repeatedly emphasized the central role of the amygdalae and insula in the neural circuitry of the disorder. Selective serotonin reuptake inhibitors (SSRI) are commonly accepted as first line therapy, however other substance classes like serotonin norepineprine reuptake inhibitors (SNRI), monoamine oxidase inhibitors (MAOI), benzodiazepines and several other agents have also proved effective. There is still a substantial lack of data on therapeutic options in cases of non-responsive SAD as well as on add-on therapy. A combined treatment-approach including psychotherapy (e.g. cognitive behavioural therapy) may prove useful.

Key words: *anxiety disorders - social anxiety disorder – pharmacotherapy - epidemiology*

ZUSAMMENFASSUNG

Sozialphobien gehören zu den häufigsten psychiatrischen Erkrankungen. Ungeachtet der hohen Prävalenz wird diese Erkrankung noch immer zu selten erkannt, diagnostiziert und und ausreichend behandelt. Das Krankheitsbild entwickelt sich typischerweise in der Kindheit oder im frühen Adoleszenzalter und zeigt häufig einen chronischen Verlauf. Die Erkrankung stellt eine massive Belastung für die Patienten dar und wirkt nicht nur in sozialen Aspekten, sondern auch im Beruf und der Ausbildung der Betroffenen behindernd. Obwohl in der Erforschung der Ätiologie der Erkrankung bereits große Fortschritte gemacht wurden, hat sich noch kein allgemein akzeptiertes Modell entwickelt. Die Daten aus genetischen Studien und Studien mit bildgebenden Verfahren deuten auf ein Mitwirken des noradrenergen, des dopaminergen und des serotonergen Systems in der Pathophysiologie hin. In funktionellen Magnetresonanztomographiestudien wurde wiederholt die zentrale Rolle von Strukturen wie den Amydalae und der Insula in der neuronalen Grundlage der Sozialphobien gezeigt. In der Therapie der Sozialphobien werden allgemein selekive Serotonin-Wiederaufnahmehemmer als Mittel der ersten Wahl betrachtet. Andere Substanzklassen wie Serotonin-Noradrenalin-Wiederaufnahmehemmer, Monoaminoxidasehemmer, Benzodiazepine und einzelne andere Psychopharmaka haben ebenfalls Therapieeffizienz bewiesen. Zum gegenwärtigen Zeitpunkt gibt es noch immer kaum Daten über Therapieoptionen bei Therapieresistenz oder über add-on Strategien. Eine weitere Möglichkeit stellen kombinierte Therapiestrategien mit psychotherapeutischen Ansätzen (z.B. kognitive Verhaltenstherapie) dar.

Schlüsselwörter: *Sozialphobie - Psychopharmaktherapie - Epidemiologie*

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INTRODUCTION

Awareness of social anxiety disorder (SAD, previously termed social phobia) has developed over the years from perception that it is no mere shyness or timidity but a clinical state, which may become chronic and possesses neurobiological and organic correlates. SAD is among the most frequent psychiatric disorders and shows a high lifetime prevalence of 12% and a 12 months prevalence of 7.1% (Kessler et al. 2005). Social fears are also common among the general population (Stein et al. 2000). A Canadian community survey showed that a considerable percentage of the interviewed persons report at least moderate difficulty in giving a speech (15%), participating in a meeting (14%) or talking to people they do not know (13%). This makes it difficult to distinguish a border between personality traits like shyness and SAD. The relatively late identification of SAD 40 years ago, as a diagnostic entity separate from the group of specific phobias might reflect this fact. Unlike commonly observed isolated social fears, this

disorder greatly affects the patient's social and professional life and relationships (Katzelnick et al. 2001) and the high disability level resulting from SAD is comparable with that observed in cases of major depression (Sheehan et al. 1996).

SAD is classified with other phobic disorders in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and in the International Classification of Diseases 10 (ICD-10). According to the criteria in the DSM-IV a patient diagnosed with SAD has to have a marked and persistent fear of one or varying social situations involving exposure to strangers or possible scrutiny by others. The sufferer is extremely afraid of doing or saying something embarrassing or humiliating, or showing symptoms of anxiety. Exposure to such situations provokes anxiety, which may even present as a panic attack and they are therefore often avoided or endured with distress although the patient realises that this fear is excessive or unreasonable. The anxious state is due neither to substance effects, nor to a general medical condition or other mental disorder. At a pathological level, SAD affects functioning in all aspects of daily life, including professional functioning, social activities and relationships.

There are two subtypes characterized in the DSM-IV which are distributed equally among patients, namely the generalized and the non-generalized (performance-type) social anxiety disorder. Persons with generalized SAD typically experience fear and show avoidant behaviour in most social situations. This subtype is reported to be more common in patients in primary healthcare (Stein et al. 1999) and is associated with more psychiatric comorbidities and functional impairment than non-generalized SAD. Individuals with performance-type SAD experience fewer social fears, with the fear of speaking in public occurring most frequently - 80% (Kessler et al. 1998).

Reported physical symptoms in patients with SAD are sweating, trembling, blushing, palpitations, nausea and diarrhoea. Patients complain of concentration difficulties, nervousness, restlessness, and show hypervigilant behaviour. Social withdrawal is often a consequence of this extreme situation-related discomfort, but unlike persons that isolate themselves willingly due to psychiatric conditions (e.g. schizoid personality disorder), persons with social anxiety disorder crave the company of others.

EPIDEMIOLOGY, COURSE AND BURDEN OF THE DISEASE

SAD shows a typically early onset in adolescence and even childhood in the case of the generalized type (Chavira and Stein 2005). A french study in primary care patients determined the mean age of onset as 15.1 years with a 90% probability of this disease developing in sufferers before the age of 25. Therefore SAD is the second most frequent anxiety disorder occurring by early adulthood (Chavira et al. 2004). Maltreatment in childhood or other traumatizing psychosocial events are apparently not associated with a childhood onset of SAD (Chavira and Stein 2005). Moreover behavioural inhibition, a heritable temperamental trait, seems to be a precursor of the disease (Hirshfeld-Becker et al. 2007). Twin studies confirm anxiety traits to be heritable (Stein et al. 2002) and moderate heritability of SAD is suggested by further family studies.

The disease generally becomes chronic and appears to be more frequent in women than men. Prevalence rates appear to be stabile in youth and adulthood and symptoms persist even in old age (Cairney et al. 2007, Kessler et al. 2005). As mentioned previously, the lifetime prevalence is approximately 12% (Kessler et al. 2005) and studies in the USA, Canada and Australia show similar rates (Iancu et al. 2006).

The harmful effects of SAD on the patient's development often begin in childhood in the form of school refusal. The association between SAD and leaving school early has been frequently shown (Stein and Kean 2000). Academic underachievement, underperformance at work or even the inability to work, reflected by higher unemployment rates in patients with SAD are among the consequences (Wittchen and Beloch 1996) resulting in a reduced quality of life (Stein et al. 2005).

SAD frequently shows psychiatric comorbidities that aggravate its detrimental effect on patient's lives. Major depression frequently accompanies the disorder (Rush et al. 2005), moreover SAD, like other anxiety disorders is a significant risk factor for developing major depression (Beesdo et al. 2007). The co-occurence of major depression and SAD has been also reported as increasing the risk of suicide (Sareen et al. 2005). High rates of alcohol and drug abuse

among SAD patients (Sareen et al. 2006) might reflect an attempt at self-medication aimed at reducing social anxiety A recent study in bipolar patients revealed that 22% of the persons observed had experienced SAD, thus revealing it as the most common anxiety disorder in this population. Patients with eating disorders also show a substantial prevalence (20%) of comorbid SAD (Hinrichsen et al. 2003).

BIOLOGY

The pathophysiology of social anxiety disorder has not yet been investigated sufficiently, however recent findings from genetic and neuroimaging studies have delivered new data that may lead to a deeper understanding of the disorder.

In 2004 the first genome wide linkage study in social anxiety patients was conducted by Gelernter et al. (Gelernter et al. 2004) suggesting linkage of chromosome 16 markers near the norepinephrine transporter protein. Heritable personality traits such as low extraversion, that often appears to be part of the psychopathology, have also been shown to be linked with a certain polymorphism of the β_1-adrenergic receptor gene (ADRB1) (Stein et al. 2004). Furthermore, Smollen et al. found a strong association of the corticotropin releasing hormone (CRH) gene and behavioural inhibition (Smoller et al. 2005), a temperamental antecedent of social anxiety in children (Hirshfeld-Becker et al. 2007), a fact supporting the importance of adrenergic neurotransmission in SAD.

The higher prevalence of anxiety disorders in patients with Parkinson's disease (Stein et al. 1990) and the lower density of dopamine reuptake sites (Tiihonen et al. 1997) suggest a dysfunction of the striatal dopaminergic system in SAD patients. Additionally, a more recent study by Schneier et al. found lower dopamine D_2 receptor binding in striatal areas (Schneier et al. 2000) in subjects suffering from social anxiety.

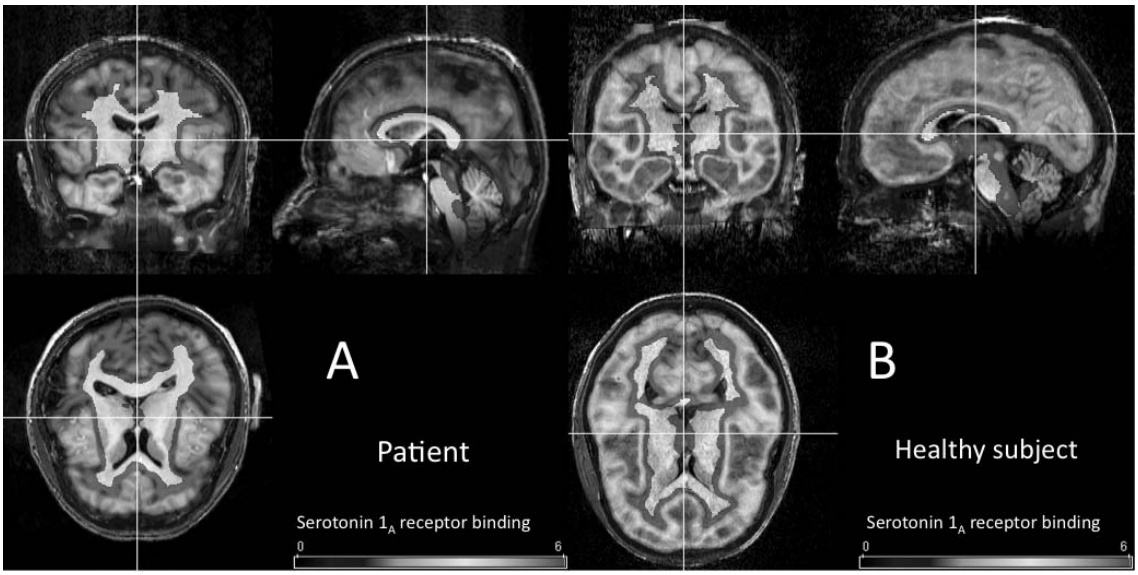

Figure 1. Serotonin-1A receptor distribution in the human brain.
The distribution was measured with PET using the radioligand (*carbonyl*-^{11}C) WAY-100635 and superimposed on magnetic resonance images. The picture shows coronal, sagittal and axial views of a male social anxiety patient (A) and a healthy male control subject (B). The colour bar indicates serotonin-1A receptor binding potential values. The serotonin-1A receptor binding is reduced across all brain regions in the patient

Genetic studies aiming at core components of serotonergic neurotransmission have also been conducted. Polymorphisms of the promoter region of the serotonin transporter (5-HTTPLR), namely the s-allele as well as a certain polymorphism in the tryptophan hydroxylase-2 gene, appear to be linked with increased activation of the amygdala, a region crucial for fear processing (Furmark et al. 2009). Regardless of conflicting results, two genetic studies focusing on shyness in children found correlations between shyness scores and 5-HTTPLR polymorphisms. Arbelle et al. reported the long form of the 5-HTTPLR (Arbelle et al. 2003) to be associated with shyness score, while Battaglia et al. found an association with the short allele (Battaglia et al. 2005). Important support for

a serotonergic contribution to the pathophysiology of SAD also comes from a recent PET study by Lanzenberger et al. comparing 5-HT_{1A} receptor binding in male patients with SAD and healthy controls (Lanzenberger et al. 2007). A direct comparison of 5-HT_{1A} receptor distribution maps is given in the figure. Patients appear to have lower receptor binding in mesiofrontal areas, the amygdala and insula, which are assumed to be part of the neural circuitry of SAD. The fact that symptom improvement, most commonly achieved with selective serotonin reuptake inhibitors, is reversible by serotonin depletion (Argyropoulos et al. 2004) also points out the key role of this transmitter in SAD.

Several functional imaging studies have been conducted in order to elucidate the functional correlates of impaired social behaviour in patients. A meta-analysis by Etkin and Wager on functional magnetic resonance imaging (fMRI) studies in anxiety disorders (Etkin & Wager 2007) shows that certain areas are hyperactive in SAD patients during emotional processing. The parahippocampal and fusiform gyrus, globus pallidus, inferior frontal gyrus, superior temporal gyrus but most consistently the amygdalae and insula were found to be hyperactive. The amygdala is thought to be the core component in the circuitry of fear and its activation appears to correlate with the severity of social anxiety symptoms (Phan et al. 2006). PET studies measuring increased regional blood flow in patients amygdalae during stressful tasks like public speaking confirm the importance of this region for the pathopysiology of the disorder. Interestingly, this phenomenon appears to be partially reversible with cognitive behavioural therapy or pharmacological treatment (Furmark et al. 2002).

TREATMENT

Despite the impairing effects of social phobia, only a minority of patients seek help and receive adequate treatment (Gross et al. 2005) although multiple pharmacological and non-pharmacological treatment options are available. Unfortunately the disorder is still underdiagnosed and undertreated as outlined over 10 years ago (Kasper 1998). The efficacy of several pharmacotherapeutic approaches has been proved in randomized placebo controlled trials. Table 1 gives a brief overview on placebo-controlled studies with different therapeutic approaches conducted in social anxiety disorder patients (Baldwin et al. 2005). A comprehensive overview on treatment options is also given in the WFSBP Guidelines for the pharmacological treatment of anxiety disorders (Bandelow et al. 2008). Most of the following cited

Table 1. Overview on treatment studies in social anxiety disorder. SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants, CBT: cognitive behavioral therapy (Baldwin et al. 2005)

	SSRIs	TCAs	Benzodiazepines	Others
Acute efficacy	Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	-	Alprazolam Bromazepam Clonazepam	CBT Phenelzine Moclobemide Brofaromine Venlafaxine Duloxetine Gabapentin Pregabalin Olanzapine
Long-term efficacy	Escitalopram Fluvoxamine Paroxetine Sertraline	-	-	CBT Phenelzine Moclobemide Venlafaxine
Relapse prevention	Escitalopram Paroxetine Sertraline	-	Clonazepam	CBT
Enhanced efficacy of psychological treatment	Sertraline	-	-	-
After non-response	-	-	-	-

studies were conducted in a double-blind placebo-controlled design in populations with generalized social anxiety disorder. The most common outcome measure in these trials is the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz 1987), providing a certain comparability of the studies. Earlier studies generally feature smaller subject numbers, while more recent trials usually include several hundred enrolled subjects. The administered drug dosages are comparable with usual dosages in major depression therapy. Interestingly no clear evidence for the therapeutic efficacy of tricyclic antidepressants can be found. Available literature also reveals a lack of efficient compounds after non-response.

MAO Inhibitors: Several early placebo controlled trials in SAD patients showed high efficacy of phenelzine, an irreversible non-selective monoamine oxidase inhibitor (MAOI) with a noteworthy difference between placebo and drug response (Heimberg et al. 1998, Versiani et al. 1992). However, the side effect profile, necessary dietary precautions to prevent hypertensive crisis and toxicity concerns limit the applicability of MAOIs. Due to the resulting poor tolerability, MAOI treatment is no longer considered as first line therapy (Versiani 2000), but presents a feasible option for non-responsive SAD patients. Reversible inhibitors of monoamine oxidase A (RIMA) have a much lower probability of increasing the pressor effect of tyramine, therefore dietary precautions are unnecessary. Moclobemide (Schneier et al. 1998, Stein et al. 2002) and brofaromine (Fahlen et al. 1995, Lott et al. 1997) have proven to exceed placebo response rates in double-blind clinical trials, yet their efficacy is thought to be inferior to MAOIs. Moclobemide, however also showed efficacy in the long term treatment of SAD (Stein et al. 2002).

SSRIS: Due to the high efficacy of selective serotonin reuptake inhibitors (SSRIs) and the favourable side effect profile, these compounds are generally regarded as first-line treatment in social anxiety disorder. The efficacy of SSRIs in the therapy of SAD has been established in more recent studies. Paroxetine was the first compound indicated in SAD treatment. A study by Stein et al. showed a significant improvement after 2 weeks of treatment that persisted and improved in a 12 week trial (Stein et al. 1998). Similar favourable results were shown by Liebowitz et al. (Liebowitz et al. 2002). Maintenance treatment and relapse prevention also appear to be feasible with this compound (Stein et al. 2002). Sertraline was approved in SAD therapy after showing a superior response rate to placebo in several placebo-controlled trials (Blomhoff et al. 2001, Liebowitz et al. 2003) for acute therapy but also for a longer therapy duration (Van Ameringen et al. 2001). A combination of sertraline and the psychotherapeutic intervention of exposure therapy may enhance the efficacy as suggested by Blomhoff et al. (Blomhoff et al. 2001). The study results for fluoxetine are not as clear, as there are two studies not showing significant results in SAD treatment when compared to placebo (Clark et al. 2003, Kobak et al. 2002). A further trial comparing fluoxetine and cognitive behavioural therapy to placebo revealed comparable efficacy for both active therapeutic approaches (Davidson et al. 2004). Fluvoxamine also exceeds placebo effects in its immediate-release (Stein et al. 1999) and controlled release form (Westenberg et al. 2004). The latter also showed long term efficacy in a 24-week trial (Stein et al. 2003). Citalopram showed efficacy in only one double blind placebo controlled study (Furmark et al. 2005) to date, whereas newer studies confirmed the efficacy of escitalopram, the therapeutic active enantiomer of citalopram. Lader et al. compared escitalopram, paroxetine and placebo and found significantly higher response rates for the active compounds (Lader et al. 2004). Similar findings were reported by Kasper et al. for escitalopram (Kasper et al. 2005). The compound was also more effective than placebo in long term treatment and relapse prevention as shown by Montgomery et al. in a 24 week trial (Montgomery et al. 2005).

Benzodiazepines: In patients with treatment-resistant SAD benzodiazepines may be a treatment option. Clonazepam has shown efficacy in double blind placebo controlled trials for acute treatment (Davidson et al. 1993, Munjack et al. 1990). There is also evidence for long term efficacy as shown by Davidson et al. (Davidson et al. 1991) in an open trial study over 11 months. A combination of clonazepam and paroxetine compared with the antidepressant alone resulted in no significantly faster response, yet a trend (i.e. 79% vs. 43 % as measured by CGI) towards a better outcome was observed in a study by Seedat et al. in 28 patients (Seedat & Stein 2004). The lack of statistical power might be the reason for not detecting a significant difference. Gelernter et al. tested alprazolam in SAD treatment, but although

patients did respond after 12 weeks, the measured response rate of 38% appeared poor (Gelernter et al. 1991). A more convincing response rate was achieved with bromazepam by Versiani et al. (Versiani 1997) suggesting an alternative treatment option of SAD. Although benodiazepines might be an additional option, drawbacks like sedation, potential of abuse and discontinuation difficulties have to be considered.

SNRIS: Venlafaxine was the first serotonin norepineprine reuptake inhibitor (SNRI) that effected significantly more treatment response than placebo in patients with SAD. Duloxetine has also been reported to be effective although there are no double-blind placebo controlled trials yet to confirm this clinical observation. Up to now only two case reports in generalized SAD (Crippa et al. 2007) and SAD with comorbid depression (Lin 2008) suggest the applicability of duloxetine in these conditions. Albeit scientific evidence for the beneficial effects of SNRIs is scarce, the known modulating effect of norepineprinergic compounds on social behaviour (Tse & Bond 2002) suggests a future perspective for duloxetine in SAD treatment.

NaSSA: Mirtazapine, a noradrenergic and specific serotonergic antidepressant showed higher efficacy than placebo in a small sample of female SAD patients (Muehlbacher et al. 2005).

$\alpha_2\delta$ calcium-channel blockers: Another second line treatment option are $\alpha_2\delta$ calcium-channel blockers. Pande et al. first evaluated the efficacy of gabapentin in a placebo-controlled trial for the first time (Pande et al. 1999) and found significant improvement in all outcome measures (e.g. LSAS, BSPS). In a second study pregabalin was shown to exert treatment effects in SAD patients, although there was no significant improvement when compared to placebo (Pande et al. 2004). These findings suggest a possible future role for $\alpha_2\delta$ calcium-channel blockers in SAD treatment.

Beta blockers: Findings in patients with performance anxiety showed a beneficial effect of this group of medication (James and Savage 1984). However, SAD patients appear not to profit from beta-blocker treatment as showed in placebo controlled trials with atenolol (Liebowitz et al. 1988, Turner et al. 1994). Furthermore, augmentation strategies with pindolol added to paroxetine in treatment resistant SAD showed also no efficacy (Stein et al. 2001). Results from subjects with isolated performance anxiety therefore cannot be generalized and applied to SAD patients and the use of beta blockers in this population cannot be recommended.

A few other pharmacological compounds such as the atypical antipsychotic olanzapine have been tested for efficacy in SAD treatment. Although this agent appears to be superior to placebo in a small pilot study (Barnett et al. 2002), the small sample size makes the results only preliminary. The neurokinin-1 antagonist GR205171 also appears to be efficient (Furmark et al. 2005), yet these findings need to be confirmed too.

Non-pharmacological treatment: Among psychotherapeutic treatment approaches, exposure therapy and CBT (cognitive behavioural therapy) showed efficacy in SAD treatment when compared to a "psychological" (Cottraux et al. 2000) or pill placebo (Davidson et al. 2004) in acute and long term treatment settings.. However, direct comparison studies with SSRI treatment show no advantage of exposure therapy (Blomhoff et al. 2001) over sertraline or difference between the efficacy of CBT and fluoxetine (Davidson et al. 2004). Therefore according to current knowledge, psychotherapeutic treatment cannot fully replace psychopharmacologic approaches. A meta-analysis of studies on drug and psychological treatment combination in anxiety disorders by Bandelow et al. however provides preliminary support for a combined approach in SAD, making possible synergistic effects of pharmacological and psychotherapeutic treatment appear likely, although this remains a matter of debate.

RECOMMENDATION FOR TREATMENT

In view of the knowledge gained from the abovementioned studies, several recommendations for treatment can be given. SSRIs have proven to be the first line treatment for SAD. MAOIs are effective to some extent, however the unfavourable side-effect profile makes these compounds only second choice. Benzodiazepines and $\alpha_2\delta$ calcium-channel blockers are also an option for second line treatment.

Stein et al. developed an algorithm for the pharmacotherapy of social anxiety (Stein et al.

2001) distinguishing between several applicable steps for primary care. Firstly, the psychiatric condition must be diagnosed following official criteria as given by classification systems such as DSM-IV and ICD-10. Secondly, and essential for further therapeutic decisions, comorbidities such as major depression, suicidality, other anxiety disorders or substance abuse must be assessed as well. If complications are present, first line therapy should be modified (e.g. detoxification in case of co-morbid substance abuse, inpatient treatment in suicidal patients). As mentioned previously, SSRIs are suitable for first line pharmacotherapy. The applicable dosages are comparable to those of major depression therapy. However, the latency of treatment response may be longer than in depressed patients and therefore the interval for the evaluation of response should be approximately 6-8 weeks. If certain side effects make treatment continuation intolerable, a switch to another SSRI or a different class of medication should be considered. Before evaluating a drug's efficacy, the dose should be optimized within the therapeutic range, and most likely should be increased. Furthermore, improvement in target symptoms such as role dysfunction ,may only be evaluable after longer observation. This results in a treatment period of up to 12 weeks before a decision on efficacy can be made. In responsive patients, dose and therapy should be maintained in order to prevent relapse. Although there is not enough evidence to make a definitive recommendation for the duration time, it is current consensus to maintain treatment for at least one year before beginning medication withdrawal. In the case of non-response, the patient's compliance, diagnosis, comorbidities and complicating psychosocial circumstances should be re-evaluated to rule out these factors before declaring the patient treatment refractory. For non-responsive patients, switching to a different SSRI or SNRI is appropriate. Due to the lack of empirical data, no definite recommendation can be given, albeit preliminary results point out venlafaxine as one possible candidate (Altamura et al. 1999). Also classic MAOIs may be effective in this subpopulation.

CONCLUSION

Social anxiety disorder is a highly prevalent psychiatric condition with mostly underestimated effects on the functionality of individuals affected. Although significant progress in the study of the epidemiology, genetics, the underlying neurobiological principles and therapy has been made, many open questions remain for future research. Primary psychiatric care will have to develop strategies in order to reach more of the population suffering from social anxiety symptoms and increase awareness of the disorder since SAD is still considerably underdiagnosed and undertreated.

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