Peer reviewed article

Selective serotonin reuptake inhibitors in children and adolescents

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Summary

This article will review the tolerability, side effects, and effectiveness of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents. We aimed to familiarise the readers with the available data on the pharmacological treatment of childhood psychiatric disorders, especially of depressive disorder and obsessive compulsive disorder. Tricyclic antidepressants (TCAs) have questionable efficacy, definite problems with safety (e.g., cardiotoxicity, lethality in overdose, anticholinergic side effects), and compliance issues. Therefore it is suggested suggest that SSRIs should be the first-line treatment for these disorders in children and adolescents. Studies have shown a significant clinical response to SSRIs and their efficiency has been demonstrated in open and controlled trials. It is often recommended that clinicians should start low and go slow when using SSRIs, and maintain the patient in a symptom-free state for at least six months. The side effects of SSRIs are generally mild, manageable, and seldom require discontinuation of treatment. Children should be monitored closely for infrequent side effects such as gastrointestinal upset, headache, and behavioural activation which may be as severe as mania. There is a great need for controlled trials in childhood psychiatric disorders, especially in anxiety disorders.

Key words: selective serotonin reuptake inhibitor; pharmacotherapy; children; adolescents; depression; obsessive compulsive disorder

Introduction

Increases in psychotropic prescriptions for children and adolescents have generated considerable controversy in the medical literature and popular press [1]. Most of the debate has centred on issues of safety, effectiveness, and prescription patterns of the psychotropic medications. Selective serotonin reuptake inhibitors (SSRIs), a subclass of antidepressants, are one of the most common types of psychotropic medications prescribed to children [2]. Jensen et al. reported approximately 1 million SSRI mentions in US in 1995 for children younger than 18 years [2]. Prescription prevalence in school-aged children 6 to 14 years increased from 0.2% to 1.5% for SSRIs [1].

Clinical interest in SSRIs stems from both these drugs' lack of anticholinergic and cardiotoxic side effects when compared with tricyclic antidepressants, and from their apparent effectiveness in diverse clinical conditions and comorbid symptoms such as depression, generalised anxiety disorder, anorexia nervosa and bulimia [3–5]. SSRIs are also considered to be safe at high doses or in situations of attempted suicide where very large doses may be ingested. SSRIs such as fluoxetine, fluvoxamine, sertraline, citalopram and paroxetine, have been reported to be effective in children and adolescents [3–30], but in contrast to their increased and wide use, well-designed controlled studies are very limited in children and adolescents.

A crucial step before recommending any treatment for childhood psychiatric disorders is a thorough evaluation of psychiatric symptoms, as well as symptoms of other comorbid psychiatric diagnoses, and associated psychosocial and academic problems [31]. In addition, a medical history and examination should be conducted and laboratory tests requested if warranted [31, 32]. Diagnostic systems (e.g., DSM-IV [American Psychiatric Association, 1994]; ICD-10 [World Health Organization, 1994]) have been developed with criteria to diminish the variability in the interpretation of symptoms and standardise diagnostic procedure [31–34]. Frequent comorbidity of psychiatric diagnosis should be taken into account when deciding on treatment, especially in instances of psychoactive drug abuse/addiction in adolescents. To reach a diagnosis standardised instruments for

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interview have been used to increase the validity and reliability such as the Diagnostic Interview for Children and Adolescents (DICA) [35], Diagnostic Interview for Children and Adolescents (DISC) [36], Child Schedule for Affective Disorders and Schizophrenia (K-SADS) [37], Interview Schedule for Children (ISC) [38], and Child Assessment Schedule (CAS) [39]. Self report scales are important instruments when assessing and following up depression, anxiety, and obsession. Some of these instruments are Children's Depression Inventory (CDI) [40], Children's Depression Rating Scale (CDRS) [41], State-Trait Anxiety Inventory for Children (STAIC) [42], Children's Manifest Anxiety Scale (CMAS) [43], Screen for Child Anxiety Related Emotional Disorders (SCARED) [44], Leyton Obsessional Inventory [45], Yale-Brown Obsessive-Compulsive Scale for Children (also includes clinician's ratings) [46], and Maudsley Obsessive Compulsive Questionnaire (MOCQ) [47]. To rate the global functioning of children by Children's Global Assessment Scale (CGAS) [48] enables the clinician to discriminate between children who have many symptoms but still function well and those who are functioning poorly either at baseline or during follow up.

Practitioners sometimes avoid giving medications to children and adolescents because they are concerned about unusual responses or dosage requirement. However, there are few qualitative differences between children and adults in response to medication. Children's younger organs frequently clear medications more quickly, and adolescents generally need adult doses. [49]. Pharmacotherapy should be a part of the treatment plan in which all aspects of the child's or adolescent's life are considered. The child and his or her family, should be evaluated at the psychiatric, social, cognitive, and educational level. Careful attention should be paid to differential diagnosis, including medical/neurological and psychological factors contributing to the clinical presentation [50].

Therapeutic intervention should be started early, before complications, chronicity, and social incapacitation occur, which can make treatment and restabilisation of functional life more difficult. Adolescents may consider the drug as a threat to their independence and may be non-compliant. Before treatment with a psychotropic drug is initiated, the family and the child or adolescent should be made familiar with the risks and benefits of such interventions, the availability of alternative treatments, and the likely adverse effects and withdrawal adverse effects [50]. The goal of pharmacotherapy is to optimise efficacy, thereby reducing morbidity and mortality, while simultaneously optimising safety [51, 52]. When starting SSRIs, it is very important to "start low, and go slow" [3, 4, 51, 52]. The clinician should maintain frequent contact (i.e., weekly) with the patient and the family during the initial phase of treatment to carefully monitor response to the intervention and side effects [50]. It is recommended to maintain the patient in a symptom-free state for at least six months, if not a year [13, 51–54]. Tapering should occur during low stress periods, and should be done very slowly to avoid relapse and withdrawal [3, 54].

Depressive disorder

Worldwide, depression is a major cause of morbidity and mortality in children and adolescents, with suicide one of the leading causes of death in children aged 8–18 [55, 56]. Most studies suggest depression in children and adolescents is the same disorder as depression in adults [57–59]. Adolescent depression carries an elevated risk of adult depression irrespective of comorbidity [57]. Improvements in the capacity to recognise, diagnose and treat depression in children and adolescents are of major public health importance [31, 32, 52]. Recognition and diagnosis is the first step [4, 31, 32].

Several case reports and open studies have suggested the efficacy of some psychosocial interventions, especially cognitive-behavioural therapy, for treatment of childhood depressive disorders [60, 61].

Antidepressant medications seem to be indicated for children and adolescents who are not responding to an adequate trial of psychotherapy; children and adolescents whose severity of depressive symptoms interferes with academic and social functioning, impeding an adequate trial of psychotherapy; patients with recurrent depression that does not respond to or cannot be prevented with psychotherapy; psychotic depression; and bipolar depression [31, 32].

In 1995, Hazell published a meta-analysis of all available placebo-controlled TCA studies (n = 12) performed in patients 6–18 years of age between 1981 and 1992 that showed no significant benefit of TCA treatment over placebo (50% to 70%) [62]. In contrast, the placebo response in depressed adults has ranged from 30% to 40%, suggesting that children and adolescents are more likely to respond to placebo than adult populations [63]. Possible factors associated with a high placebo response in children and adolescents include the following [31, 32, 63, 64, 66]: (1) the instability of affective symptoms in young populations; (2) the inclusion of patients with mild to moderate depression; (3) the lower prevalence of melancholic depression among children and adolescents; and (4) the high prevalence of comorbid conditions, particularly disruptive disorders. It is

important to note that despite the fact that many children and adolescents respond to placebo, a follow-up study showed that placebo responders had depression recurrences as frequently as non-placebo responders and patients who responded to nortriptyline [65].

SSRIs are efficacious for the treatment of adults with depression [67]. Retrospective reviews of medical records showed 74% clinical response with fluoxetine, and 64% response to sertraline in childhood depression [4, 30]. Open studies have reported significant clinical response (60% to 100%) to SSRIs for the treatment of children and adolescents with depression. In these studies; 10 to 30 mg/day fluoxetine was used for 24 weeks (n:8, aged from 5 to 18 years) [11], 110 mg/day sertraline was used for 12 weeks (n:13, aged from 12 to 18 years) [23], 50–200 mg/day sertraline was used for 22 weeks (n:53, aged from 12.2 to 19.8 years) [7], 100–300 mg/day fluvoxamine was used for 8 weeks (n:8, aged from 13 to 18 years) [8], 20–40 mg/day paroxetine was used for 9 weeks (n:7, aged from 14.7 to 18.4 years) [21], and 16.22 mg/day paroxetine was used for 8.4 months (n:45, aged 8.5 to 12.5 years) [24].

Placebo-controlled trials, which remain the standard against which efficacy is determined, number only three, two with fluoxetine and one with paroxetine. The result of a small study by Simeon et al. was negative, although improvement on Hamilton Depression Rating Scale was significantly better under fluoxetine than placebo (60 mg/day fluoxetine for 8 weeks, n:40, aged from 13 to 18 years) [5]. In contrast, a large-scale trial by Emslie et al. showed a 23% drug-placebo difference in overall clinical improvement (rated "much" or "very much" improved on the Clinical Global Impressions scale) and significant differences were also noted in weekly ratings of the Children's Depression Rating Scale-Revised after 5 weeks of treatment. (20 mg/day fluoxetine for 8 weeks, n:96, aged from 7 to 17 years old) [66]. Paroxetine was compared to imipramine and placebo (20–40 mg/day paroxetine vs. 200–300 mg/day imipramine vs. placebo) in an 8 week study with 275 adolescents (aged from 12 to 18 years), and there were 63% paroxetine-responders based on achieving a Hamilton Rating Scale for Depression (HAM-D) total score of <=8 at end-point compared to 50% imipramine-responders and 46% placebo-responders [17].

Depression is a disorder prone to frequent recurrence [32]. Furthermore, following psychopharmacological treatment or after successful psychotherapeutic treatment, depression has a high rate of recurrence (40% in two years and 70% in five years), indicating the need for psychotherapeutic and/or pharmacological maintenance treatments [32, 64, 65]. Maintenance treatment has been recommended for adults with three or more episodes of depression and for patients with two episodes who have one or more of the following criteria [68]: (1) a family history of bipolar disorder or recurrent depression; (2) early onset of the first depressive episode (before age 20); and (3) both episodes were severe or life-threatening and occurred during the past 3 years. The guidelines are also needed for depressed children.

Anxiety disorders

Anxiety is defined as apprehension, tension, or uneasiness from anticipation of danger, the source of which is largely unknown or unrecognised [69]. Fear and anxiety are common experiences across childhood and adolescence [70], forming part of adaptive management and development of coping strategies. The clinician evaluating childhood anxiety disorders faces the task of differentiating normal, transient, and developmentally appropriate anxiety from pathological anxiety [70]. Anxiety is regarded as pathological when it interferes with achievement of desired goals, quality of life, or emotional comfort [69]. Clinicians need to maintain a high level of suspicion for anxiety disorders when evaluating children. Anxiety disorders are not rare and they often mimic or are comorbid with other anxiety disorders [70].

Research on pharmacological treatments for childhood anxiety disorders remains in its infancy, with few trials using placebo controls, double-blind design, adequate medication doses, and/or well-defined, homogeneous patient populations [51]. Thus, clinicians treating anxious children are left without systematic treatment guidelines [51]. Unfortunately, it seems likely that economic, structural, and ethical factors will continue to limit work in this area [51].

In regard to the limitations of pharmacotherapy, studies of psychotherapeutic treatments of childhood anxiety disorders have been conducted. Kendall et al. detailed cognitive-behavioural therapeutic approaches for anxious children [71]. Behavioural therapy is the treatment of choice for simple phobias [51], but they are not included in this review of the pharmacological treatment of childhood anxiety disorders.

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is characterised by persistent, intrusive thoughts and images (obsessions) and repetitive, ritualistic behaviour that the individual feels driven to perform (compulsions) [33]. The symptoms of OCD often overwhelm the individual, interfering substantially with social and occupational functioning [72]. Obsessive-compulsive disorder (OCD) occurs in as many as 2% to 4% of juveniles [73]. From a pharmacological standpoint, similar to adults OCD is probably the best studied of all paediatric anxiety disorders and the condition currently most amenable to drug therapy [51]. Pharmacotherapy is an important component of the multimodal treatment of children and adolescents with OCD [53]. In the United States, two selective serotonin reuptake inhibitors (SSRIs), sertraline (ages 6–17 years) and fluvoxamine (ages 8–17 years), and the tricyclic drug clomipramine (ages 10–17 years) are approved for the treatment of OCD in children and adolescents [13]. The SSRIs are considered first-line agents, while clomipramine is considered a second-line agent because of its side effect profile (anticholinergic, antihistaminergic, and antiadrenergic) [13].

Retrospective review of medical records showed significant improvement with 50 mg/day fluoxetine in 34 children (aged from 6 to 18 years) [15]. Open-label studies in children and adolescents with OCD revealed significant improvement with fluvoxamine (100–300 mg/day for 8 weeks, n:14, aged from 13 to 18 years) [8]; citalopram (40 mg/day for 10 weeks, n:23, aged from 9 to 18 years) [29], paroxetine (20.7 mg/day for 12 weeks, n:47, aged from 9 to 15 years, and 41.1 mg/day for 12 weeks, n:20, aged from 7 to 17 years) [3, 28], and sertraline (50–200 mg/day for 52 weeks, n:137, aged from 6 to 18 years) [13]. Four placebo-controlled studies significantly favoured SSRIs in childhood OCD including Riddle's study with fluoxetine (44% reduction with 20 mg/day fluoxetine for 20 weeks on Children's Yale-Brown Obsessive Compulsive Scale vs. 27% reduction with placebo, n:14, aged from 8 to 15 years) [25], Geller's study with fluoxetine (20–60 mg/day fluoxetine for 13 weeks was significantly more effective than placebo on Children's Yale-Brown Obsessive Compulsive Scale, n:103, aged from 7 to 17 years) [16], fluvoxamine (42% responders on 50–200 mg/day fluoxetine for 12 weeks vs. 26% responders on placebo, n:120, aged from 8 to 17 years) [26], and sertraline (200 mg/day sertraline for 12 weeks was significantly more effective than placebo on Children's Yale-Brown Obsessive Compulsive Scale, n:107, aged from 6 to 18 years) [20].

Few data are available regarding the long-term efficacy and tolerability of pharmacotherapy, as well as its impact on relapse prevention in OCD patients [72]. High rates of relapse were reported in adults following the discontinuation of selective serotonin reuptake inhibitors (SSRIs) at varying time periods for up to 1 year after initiating therapy [72]. The current literature recommends that pharmacotherapy should be continued for a further 9 to 18 months after a satisfactory acute treatment response [53].

Other anxiety disorders

SSRIs were reported to be effective in almost all anxiety disorders (e.g., panic disorder, PTSD) of adults, but data is limited in children [74–77]. Generalised anxiety disorder has received little attention from paediatric psychopharmacologists. Twenty-one patients with overanxious disorders, social phobia, or separation anxiety disorder, who were unresponsive to previous psychopharmacological and psychotherapeutic interventions, were treated openly with fluoxetine (10 to 60 mg/day, mean 25.7 mg/day) for up to 10 months [9]. Eighty-one percent (n = 17) of patients showed moderate to marked improvement in anxiety symptoms. The severity of anxiety as measured by the Clinical Global Impression (CGI) was also significantly reduced from marked to mild [9]. Three case reports revealed the positive effects of citalopram in children with panic disorder and school phobia [19]. In a retrospective chart review with a mean 23.9 ± 9.8 mg/day paroxetine for 11.7 ± 8.3 months, in 18 children with panic disorder, fifteen patients (83.3%) were considered responders (CGI-Improvement scores of 1 or 2) [22]. An open study with 123.21 ± 37.29 mg/day sertraline in 14 children and adolescents (aged from 10 to 17 years) with social anxiety reported that 64% of the subjects were classified as treatment responders (36%) or partial responders (29%) as measured by the Clinical Global Impressions Scale (CGI)-improvement subscale by the end of the 8-week [12]. Post-traumatic Stress Disorder (PTSD) is a syndrome defined by the intrusive re-experiencing of a trauma, avoidance of traumatic reminders, and persistent physiological arousal. PTSD is associated with high levels of comorbidity and may increase the risk for additional disorders over time [78]. Medication treatments can be effective in PTSD, acting to reduce its core symptoms, and should be considered as part of the treatment of this disorder. The existing evidence base does not provide sufficient data to suggest a particular treatment strategy or predictors of response to treat-

ment [78]. In a preliminary, 12-week open-label study, eight adolescents with moderate to severe post-traumatic stress disorder (PTSD) were treated with citalopram in a fixed daily dose of 20 mg and core PTSD symptoms (re-experiencing, avoidance, and hyperarousal symptoms) showed statistically significant improvement at week 12 on the Clinician-Administered PTSD Scale (Child and Adolescent Version) (CAPS-CA), with a 38% reduction in total scores between baseline and endpoint [77].

Other disorders

A case report showed the positive effects of fluoxetine in a child with mutism [79], and Black and Uhde [10] reported a 12-week, double-blind, placebo-controlled trial of fluoxetine in 15 children and adolescents (aged from 6 to 11 years) with elective mutism and either social phobia or avoidant disorder. There was only a significant difference, favouring fluoxetine, on parents' ratings of mutism change and global change [10]. Twenty-one children with mutism (aged from 5 to 14 years) participated in a 9-week open trial of fluoxetine in graduated doses (mean end dose 28.1 mg, range 10 to 60 mg) [80]. After fluoxetine treatment, 76% were improved, with diminished anxiety and increased speech in public settings, including school.

There are very few reports in children and adolescents with eating disorders which reported little benefit of SSRIs [81, 82], although SSRIs are shown to be effective in adults in the treatment of these disorders such as binge-eating, bulimia, and anorexia [83, 84].

Few case reports and studies reported that SSRIs were effective in comorbid psychiatric disorders, such as attention deficit hyperactivity disorder, Tourette's disorder [85, 86], impulse control disorders [3, 52], and self-injurious behaviour [87], whereas SSRIs might result in increased activity or exacerbate ADHD in some cases [8, 23, 66, 88].

Safety

In general, 10–20% of adolescent patients may be expected to experience adverse events during SSRI treatment, including gastrointestinal disturbance, headache, dizziness, initial insomnia, and behavioural activity [3–30]. Most of the side effects were mild, tolerable, and decreased with time [3–30]. Studies using TCAs have provided ambiguous efficacy data and less attractive tolerability data, including the potentially fatal consequences of TCA overdose. Thus, SSRIs should be considered the first-line treatment option in children and adolescents [64].

Statistically significant but clinically insignificant differences in weight change and blood pressure were noted in Geller's study [16], although most of studies in children and adolescents reported no change in weight, vital signs including blood pressure, and lab values including ECG [3–15]. SSRIs were well tolerated with a rate of discontinuation for adverse events similar to or slightly higher than that of placebo [5, 16, 17, 20, 25, 26, 66].

Mania and hypomania can result from treatment with any of the antidepressants, including the SSRIs [8, 18, 23]. There are reports of at least nine cases of children or adolescents in whom mania developed during SSRI therapy; some had a family history of affective disorder [18, 23], four children with OCD also developed manic symptoms on SSRIs [8, 88]. There was a grand mal seizure in a 15-year-old female who had a history of Guillain Barré syndrome with sensorineural hearing loss, that led to discontinuation from a sertraline open-label study [13].

It is reported that SSRI discontinuation syndrome does and can occur in children when an SSRI is stopped or reduced, and is quite similar to adult reports. Clinician needs to be aware of potential symptoms associated with an SSRI discontinuation syndrome in a child treated with SSRIs, either during treatment (as a result of missed doses or noncompliance), or when stopping treatment [54].

A large number of drugs from different therapeutic classes are dependent on CYP 2D6 enzyme for their metabolism including tricyclic antidepressants, codeine, β-blockers, Type IC antiarrhythmics and several antipsychotics [3, 14, 54]. Either due to drug inhibition of CYP 2D6 (substantially by fluoxetine and paroxetine, mildly by sertraline) or genetic polymorphism (causes genetically poor drug metabolisers) may possibly bring up toxic increases of the concentration of the concurrent drug such as tricyclic agents [3, 14]. Antidepressants and antipsychotic drugs are also metabolised by CYP 2D6 enzyme and therefore should be used cautiously with fluoxetine and paroxetine [3, 54]. One of the two children who developed hypomania early in the course of the paroxetine trial was a poor cytochrome P450 2D6

(CYP 2D6) metaboliser [14]. In addition, 5 to 10 percent of white persons possess an autosomal recessive genetic defect in the expression of the isoform CYP 2D6, making them poor metabolisers [14]. The CYP 3A ¾ system is inhibited moderately by fluvoxamine and mildly by fluoxetine, and use of drugs that are metabolised by CYP 3A ¾ (e.g., carbamazepine, tricyclic agents, clozapine, and benzodiazepines) requires caution given the risk of increased concentration of the latter drug [3, 54]. Our current knowledge suggests that fluoxetine possibly inhibits the CYP-2C 9/10 system, that the -2C 19 and -3A ¾ systems are mildly inhibited, and substantially inhibits the -2D6 system; fluvoxamine inhibits the CYP-1A2 system substantially, whilst moderately inhibiting -2D6 and 3A ¾ systems; paroxetine substantially inhibits the CYP-2D6 system, sertraline mildly inhibits the CYP-2D6 system, and citalopram is metabolised via the CYP-2C19 system [3, 14, 54]. Any drug that is being metabolised by these systems should be given cautiously with the involved SSRI and clinicians should always check the most recent data (e.g., updated psychiatry web pages) which represents drug interactions before prescribing a concurrent medication.

The pharmacokinetics of sertraline [plasma concentration-time curve (AUC), peak plasma concentration (C_{max}), and elimination half-life ($t_{½}$)] were similar in patients aged 6 to 17 years to those reported for adults [6], but there is a need for more pharmacokinetic studies of SSRIs in children and adolescents. We also know little about drug-drug interactions in children, an area that needs further clinical attention.

Conclusion

Some authors have raised concerns about increases in prescription rates of psychotropic medications in children and adolescents including SSRIs, and potential overuse, inappropriate prescriber practices, and substitution for counselling or comprehensive therapy [89, 90]. Potential positive influences of increased recognition and treatment of previously unrecognised mental disorders, improvements in access to psychiatric care, or increased education about the proper use of these medications must also be considered along with concerns of harmful effects and negative associations with expansion of prescription use [1].

Studies using SSRIs have shown them to be effective and well-tolerated in children and adolescents especially in depression and anxiety disorders. SSRIs should be the first-line treatment in children and adolescents since TCAs have questionable efficacy and definite problems of safety [52]. The high degree of comorbidity, psychosocial and academic consequences of depression and anxiety disorders in childhood also emphasise the importance of a multimodal treatment approach which includes pharmacotherapy [31, 32]. Pharmacotherapy should not be used instead of other interventions or merely where other interventions have failed [50]. There continues to be a need for information from double-blind, placebo-controlled trials in the paediatric population regarding the safety and efficacy of pharmaceutical agents for the treatment of childhood psychiatric disorders.

In addition to safety, psychotropic prescription trends and changes in mental health care also have important implications for the cost of care. New psychotropic medications like the SSRIs are expensive, yet favourable cost studies of SSRI use in long-term treatment in adults have not been documented for paediatric patients [1]. The effects of psychotropic prescription practices on use of other services (inpatient hospitalisations, counselling, and medical services), medical and mental health expenditure, and long-term outcomes for children and their families should be the subject of the further research.

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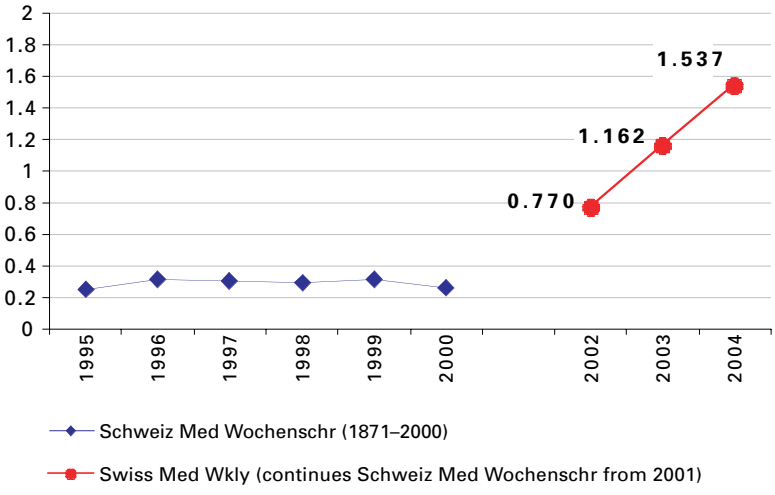

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