

CLINICAL PRACTICE GUIDELINE

The Treatment of Depressive Disorders in Children and Adolescents

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SUMMARY

Background: Depressive disorders are among the more common mental illnesses around the world. About 3% of prepubertal children and 6% of postpubertal children and adolescents are affected. Many physicians are unsure about which treatment approaches are effective and how the treatment should be planned.

Methods: A systematic literature search was carried out in electronic databases and study registries and as a manual search. More than 450 studies (mostly randomized controlled trials [RCTs]) were identified and summarized in five evidence tables. The ensuing recommendations were agreed upon in a consensus conference in which 23 organizations were represented.

Results: The recommended treatment of first choice for children from age 8 onward and for adolescents is either cognitive behavioral therapy (CBT) (Cohen's d [effect strength]: 0.5–2) or interpersonal psychotherapy (Cohen's d: 0.5–0.6). Fluoxetine is recommended for drug treatment (Cohen's d: 0.3–5.6), either alone or in combination with CBT. The analysis revealed a lower level of evidence for psychodynamic or systemic psychotherapy or for drug treatment with escitalopram, citalopram, or sertraline. For mild or moderate depression, psychotherapy is recommended; for severe depression, combination therapy. Particularly for children, there is a lack of adequately informative comparative studies on these treatment approaches as well as on other, complementary interventions (e.g., art therapy, sleep deprivation, youth welfare services).

Conclusion: There is adequate evidence to support some recommendations for the treatment of depressive disorders in adolescents, but evidence for children is lacking. There is a pressing need for intervention research in this area for both children and adolescents.

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Depressive disorders are among the more common mental illnesses all over the world, with an estimated 121 million sufferers, according to the World Health Organization (WHO). Depressive disorders are currently the single most important cause of “years lost due to disability” (YLD—a statistical measure of years lived with a disability, multiplied by the severity of the disability). It is projected that, by the year 2020, depressive disorders will also become the second most important cause of loss of “disability-adjusted life years” (DALY) (WHO, 2012) (1).

Depressive disorders can arise early in life: some 3% of prepubertal children and 6% of postpubertal children and adolescents are affected (e1). These disorders manifest themselves in episodes of varying duration and are often chronic. They markedly impair psychosocial development. An adolescent who has had one episode has a 50% to 70% chance of having a second one within five years (e2).

Not all of the affected children and adolescents receive optimal treatment (2). For many of the currently available treatment options, evidence of efficacy is lacking. Recommendations about the treatment of depressive disorders in adults (e3) do not necessarily apply to younger patients, as both the manifestations of disease and the appropriateness and efficacy of various forms of treatment depend on the patient's age and level of development.

In 2010, the German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (*Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie*, DGKJP) initiated a project to develop a new evidence- and consensus-based S3 guideline for the treatment of depressive disorders (ICD-10 codes F32, F33, F34.1 and F92.0) in children and adolescents (ages 3–18), so that more of these younger patients can receive optimal treatment. The guideline contains information on the current state of scientific knowledge about treatment and gives recommendations for the selection and planning of effective treatment strategies (3).

Methods

A systematic search for existing guidelines (*Figure 1*) yielded three of these (4–7). In addition, searches for relevant publications that appeared from July

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2011 to July 2012 were carried out in each of four databases, in clinical trial registries, and (by manual search) in scholarly periodicals and congress proceedings. Modular search filters were used (for an example, cf. *eBox 1*). Two independent judges selected and evaluated the studies; when their opinions diverged, they reconsidered and discussed the study in question until they reached agreement. Inclusion and exclusion criteria are listed in the *Box*.

All systematic reviews and controlled trials were evaluated by the two judges with the aid of the structured checklists of the Scottish Intercollegiate Guidelines Network (SIGN, available at www.sign.ac.uk/methodology/checklists.html). They were then thematically grouped and summarized in five evidence tables and assigned levels of evidence. The evidence tables and the previously published guidelines were used to develop recommendations for key clinical questions; each recommendation was stated together with a recommendation grade. Evidence levels and recommendation grades were assigned according to the scheme of the Oxford Centre for Evidence-Based Medicine (8) (*eTable*).

In a consensus conference moderated by the Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF), every recommendation was discussed in a “nominal group process” and then voted on. Each of the 23 participating organizations (*eBox 2*) had one vote. Each recommendation was issued with a “strong consensus” (>95% agreement), by “consensus” (>75–95% agreement), or by “majority agreement” (>50–75% agreement).

Results and recommendations

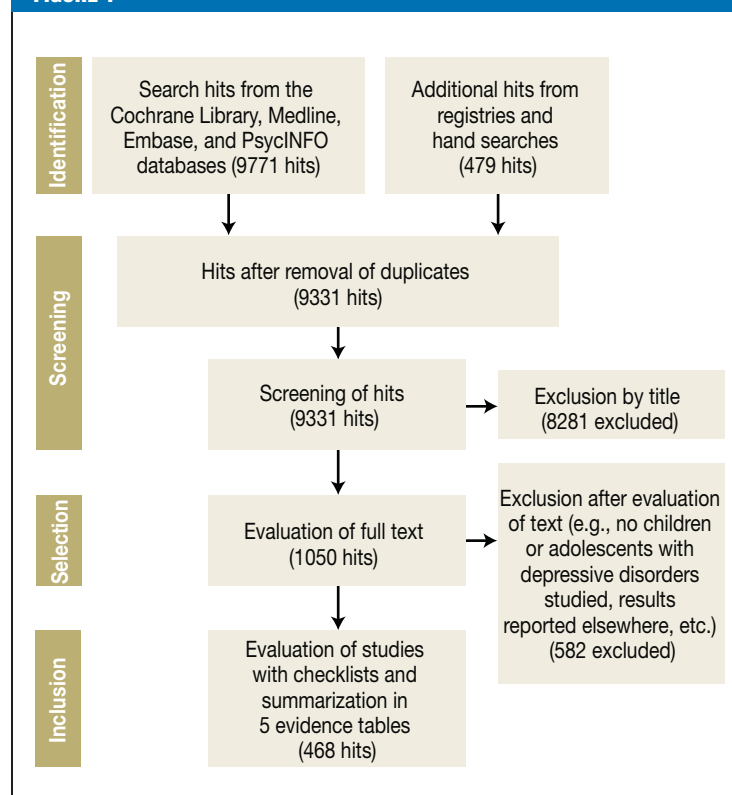
Treatment setting

The first necessary step in the treatment of depressive disorders is thorough diagnostic evaluation and classification according to the ICD-10 criteria. The ICD-10 distinguishes three degrees of severity of depressive episodes: mild, moderate, and severe (*Figure 2*). A mild depressive disorder without comorbidity, significant risk factors, a family history of affective disorders, or warning signs of a likely relapse can be initially managed with watchful waiting for six to eight weeks. This includes support in coping with everyday tasks and counseling or psychoeducation about the manifestations of the disorder, its causes, the expected course, and the options for treatment.

Follow-up evaluations should be performed every two weeks. This recommendation also applies to children and adolescents who refuse treatment, as well as to those who are fully able to cope with the demands of everyday life as appropriate for their age group (clinical consensus point [CCP], recommendation issued by consensus).

As a rule, children and adolescents with depressive disorders are treated in the outpatient setting. A

FIGURE 1



Results of the systematic literature search and evaluation

prerequisite for outpatient treatment is an appropriate level of psychosocial function (axis VI of the Multi-Axial System [MAS]) (9) (CCP, strong consensus). This means, among other things, that the patient must be able to maintain contact with other persons and cope with everyday tasks, such as regular school attendance. On the other hand, reasons for hospitalization include the following:

- acute suicidality, together with the inability to adhere to a non-suicide agreement (i.e., the patient cannot be counted on to seek help if suicidal thoughts arise);
- a depressive disorder that is so severe that the patient cannot (for example) attend school any more;
- inability to cope with everyday tasks, such as eating and drinking regularly or maintaining a normally structured timetable (getting up in the morning, going to bed at an appropriate time).

These criteria are represented in summary fashion on Axes IV and V of the MAS (9) (CCP, strong consensus). Day hospital care should be considered and, in some cases, recommended in the light of the severity of the episode, the patient's familial and social resources, and the local conditions of care (CCP, strong consensus).

BOX

Methods of the systematic literature search

Inclusion criteria

- Publications on the treatment of children and/or adolescents (age 3–18) with a depressive disorder diagnosed according to a classification system
- Language: English, German, or French

Systematic reviews:

- Time period: 1 January 1991 to 2012
- Systematic nature of the review: description of method, specifying (at least) the databases that were searched and the inclusion/exclusion criteria for primary studies
- > 50% of the publications included for review concern children and adolescents with depressive disorders, or else separate results are available for this patient group

Primary studies:

- Goal of the intervention: reduction of depression and/or suicidality
- >50% of the persons included in the study were children and adolescents, or else separate results are available for this patient group

Exclusion criteria

- Publications on other types of mental illness (e.g., bipolar disorders)
- Publications on depression in association with pregnancy or childbirth
- Publications limited to preventive interventions in children and/or adolescents who are not at risk, or at risk, or subclinically affected

Treatment recommendations

Data on the efficacy of psychotherapy are available mainly for adolescents (over age 12). There have been very few studies of German-language psychotherapy programs; there has not been any randomized controlled trial (RCT) to date, and very few studies have directly compared different psychotherapeutic approaches. Cognitive behavioral therapy (CBT) is the type of psychotherapy that has been most commonly studied in RCTs. Psychotherapeutic interventions of all kinds have been found to lessen depression more effectively over the short term (mean, 12 weeks) in children and adolescents (age 6–18) than various alternative management strategies, both active and inactive. This is the case for all degrees of severity of depression, with a trend toward a more marked effect in moderate or severe depression. Further follow-up of the results for up to 24 months yielded inconsistent findings with respect to efficacy. As for suicidality in adolescents, no difference was found between psychotherapeutic

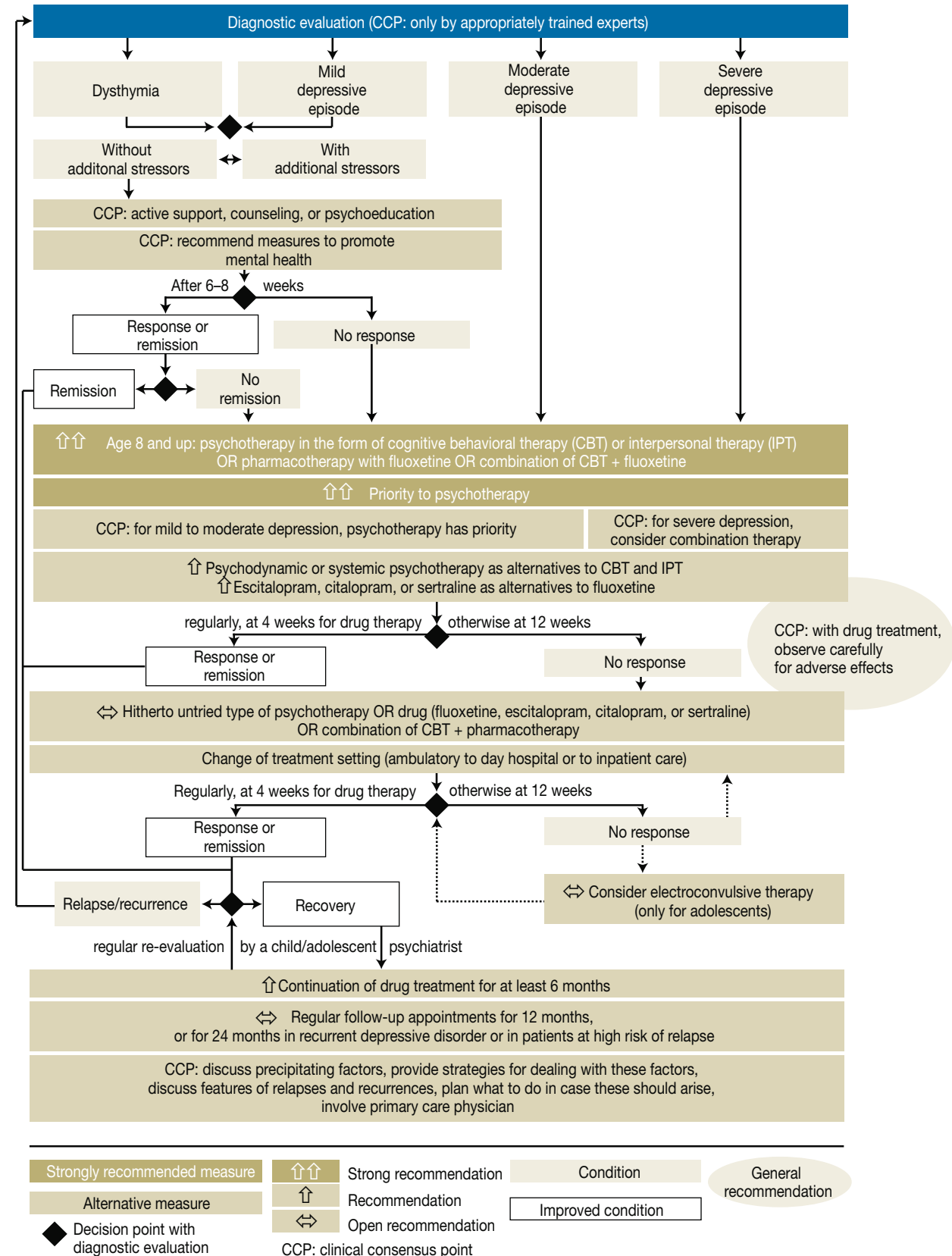
intervention on the one hand and control treatment (or no treatment) on the other, although there was a nonsignificant trend toward a greater reduction of suicidality under psychotherapy. The treatments with the highest levels of evidence to date (10, 11) are CBT (with effect strengths [ES] measured by Cohen's *d* ranging from 0.5 to 2, depending on the sample, the treatment strategy, the age of the patient, the duration of treatment, and the year of performance of the trial) and interpersonal psychotherapy (10). The latter, however, is not among the guideline techniques in Germany (with ES measured by Cohen's *d* ranging from 0.5 to 0.6, depending on the method of assessing treatment outcome).

Fluoxetine is the only drug approved in Germany for the treatment of depressive disorders in children and adolescents aged 8 and above (ES measured by Cohen's *d* in the range of 0.3 to 5.6, depending on the method of assessing treatment outcome) (e4). The recommended treatment of first choice for older children and adolescents with depressive disorders of various degrees of severity, and for those with a first episode of a depressive disorder, is either CBT, or interpersonal psychotherapy, or fluoxetine, or a combination of CBT and fluoxetine (12, 13) (strong recommendation, recommendation grade A). Some of the individual associations that belonged to the consensus group (bvvp, bkj, DGSF, BDP, BApK and BAG KT [abbreviations explained in *eBox* 2]) recommend the use of selective serotonin reuptake inhibitors (SSRIs) as second-line treatment. For mild to moderate depression, psychotherapy should initially be given priority (CCP).

In view of the adverse effects of SSRIs (headache, vomiting, sleep disturbance, fatigue, and loss of appetite at the start of treatment) and their tendency to reinforce suicidal ideation, psychotherapy should be initiated preferentially (e4) (strong recommendation, recommendation grade A). Moreover, it is recommended that patients should be closely observed for adverse drug effects and that the recommended follow-up investigations should be performed (CCP). The initial dose of fluoxetine should be 10 mg/day, and the dose can be raised to 20 mg/day at the end of one week of treatment (4). Other SSRIs should be given initially at half the daily dose for adults, and the dose can then be increased to the full recommended adult dose over the ensuing 2 to 4 weeks. Lower doses can be considered for small children, while higher doses can be considered for older children with near-adult body weight, or if a rapid therapeutic response is desired. These recommendations are largely based on the dosages that have been tested in RCTs, which are also summarized in the *Table*.

If CBT or interpersonal psychotherapy is not possible for an older child or adolescent, or if an offer of such treatment has been refused, psychodynamic or systemic psychotherapy is recommended as an alternative (recommendation grade B; evidence

FIGURE 2



Treatment algorithm based on the recommendations of the guideline “The Treatment of Depressive Disorders in Children and Adolescents” (3)

level 3–4 for both psychodynamic psychotherapy [e5–e7] and systemic psychotherapy [e7, e8]).

If treatment with fluoxetine is not possible or not desired, escitalopram, citalopram, and sertraline are recommended as alternative drugs (recommendation grade B, evidence level 1 [e4, e9]).

Treatment with tricyclic antidepressants is not recommended, as these have been found to be no more effective than placebo (evidence level 1–2 for amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline [e10–e13], evidence level 2–3 for nefazodone [e13, e14]) (strong recommendation, recommendation grade A). Nor should paroxetine, venlafaxine, or mirtazapine be given to children and adolescents with depressive disorders, as these have not been found any more effective than placebo but are associated (particularly venlafaxine) with increased suicidality (evidence level 1 [e4], strong recommendation, recommendation grade A). Moclobemide (a monoamine oxidase inhibitor, MAOI) should not be given to these patients either, as there is no evidence to support its use for this indication (evidence level 3 [e15], recommendation, recommendation grade B).

After a period of remission (i.e., absence of clinically relevant manifestations) of at least two months' duration, drug treatment should be continued for at least six more months (recommendation, recommendation grade B), as it has been shown, for example, that 24–32 weeks of treatment with fluoxetine pre-

vents and delays relapses in children and adolescents (aged 7–18) more effectively than placebo (evidence level 3 [e16, e17]). Likewise, the prolongation of CBT for a further six months after ten weeks of acute treatment has been found to be associated with a lower cumulative risk of relapse than management in a control group (evidence level 4 [e18]).

Discontinuation of drug treatment can be considered when there has been a period of remission of at least six months' duration after the first episode of a depressive disorder (CCP). The results of treatment should be regularly rechecked by a child and adolescent psychiatrist (CCP).

Treatment approaches with inadequate evidence

Other treatments that are used in current clinical practice include the following:

- client centered psychotherapy
- art and music therapy
- ergotherapy
- youth welfare services
- repetitive transcranial magnetic stimulation (rTMS)
- vagus nerve stimulation
- sleep deprivation
- massage.

None of these methods are supported by adequate evidence, however, as clinical trials are either lacking or methodologically flawed (e.g., because of a lack of case definitions according to a classification

TABLE

Dosages of the recommended drugs that were used in randomized controlled trials

Drug - Trials	Age (years)	Initial dose (mg/day)	Maximal dose (mg/day)	Mean dose (mg/day)	Standard adult dose (mg/day), according to (14)
Fluoxetine					
– Almeida-Montes 2005 (e26)	8–14	20	20	20	20–40
– Emslie 1997 (e2)	7–17	20	20	20	
– Emslie 2002 (e27)	8–17	10 in week 1	20	20	
– Simeon 1990 (e28)	13–18	20 in week 1, 40 in week 2	60	unknown	
– TADS 2004 (e29)	12–18	10 initially, 20 in week 1	40	33.3*	
Escitalopram					
– Emslie 2009 (e30)	12–17	10 in weeks 1–3	20	13.2	10–20
– Wagner 2006 (e31)	6–17	10 in weeks 1–4	20	11.9	
Citalopram					
– von Knorring 2006 (e9)	13–18	10	40	26	20–40
– Wagner 2004 (e32)	7–17	20 in weeks 1–4	40	24	
Sertraline					
– Wagner 2003 (e33)	6–17	25 initially, 50 in weeks 1–2	200	131	50–200

*mean highest dose

scheme, lack of standardized inclusion criteria, or lack of standardized assessment of treatment outcome). Thus, no recommendation can be given for or against any of these methods (strong consensus).

The putative efficacy of the botanical substance St. John's wort (*Hypericum perforatum*) has not been documented in any controlled trial. Potential adverse effects militate against the use of St. John's wort (agitation, dry mouth, nightmares) or agomelatine (headache, dizziness, migraine, nausea, diarrhea).

There have not been any comparative clinical trials of electroconvulsive therapy (ECT) versus other types of intervention. There have been uncontrolled trials of ECT for children and adolescents who have not responded to drug treatment, many of whom have also had further complications or comorbidities. Thus, ECT cannot be recommended for children; for adolescents, it can be considered in very severe cases of depression in which the other approaches recommended in this guideline have already been tried without success (evidence level 4–5 [e.g., e19–e21], recommendation grade 0).

Results of treatment

When the treatment is begun, its goals should be clearly set and discussed with the child or adolescent patient and his or her parents, guardian(s), and/or other involved persons. The outcome of treatment should be regularly rechecked. After at least four weeks of treatment, the interim outcome can be assessed by the patients themselves (e.g., with self-assessment questionnaires such as the Depression Test for Children [*Depressionstest für Kinder*, DTK], e22), by involved persons such as parents (e.g., with the FBB-DES questionnaire, e23), and by the treating specialist (e.g., with the Kinder-DIPS clinical interview, e24). If there has been no clinically significant improvement after 12 weeks of treatment, or if there has been no response to drug treatment (a significant reduction of depressive manifestations for at least one week) in four weeks, then the treatment modality can be changed (CCP, strong consensus).

Children and adolescents with depressive disorders who have no improvement after the first treatment attempt can be treated with a different type of psychotherapy, or with a different medication than the one initially used, if any (fluoxetine, escitalopram, citalopram, or sertraline), or else with a hitherto untried combination of CBT and one of the medications just mentioned. A switch from outpatient treatment to day hospital care or to inpatient treatment can also be considered, according to the recommendations of this guideline (evidence level 5, open recommendation, strong consensus). For older adolescents with a recurrent depressive disorder, the national care guideline for adults with unipolar depression (e3) should be applied (CCP).

A child or adolescent with a depressive disorder who is in remission, i.e., has had no clinically rel-

evant manifestations for at least 2 months, should have regular follow-up by the treating specialist for at least 12 months (open recommendation, strong consensus). A child or adolescent who is in remission after having had two or more episodes of a depressive disorder, or who is at increased risk of relapse because of stress factors that are still present, should have regular follow-up by the treating specialist for at least 24 months (evidence level 5, expert opinion).

Relapse prevention

The continuation of treatment serves to prevent, or at least delay, relapses and recurrent episodes. It was found in a randomized controlled trial of combination therapy to prevent relapses in adolescents that the risk of a relapse was significantly lower if CBT was given for 36 weeks than if fluoxetine was continued without any accompanying CBT (evidence level 3; this RCT did, however, have certain methodological flaws [e25]). As the evidence to date still does not seem to permit any definitive conclusion, the pertinent clinical consensus point (CCT) was stated in terms of “good clinical practice”: persons treating children and adolescents with depressive disorders should

- develop strategies, together with the patients and their families and other involved persons, for the prevention of relapses and recurrent episodes (CCP, strong consensus);
- inform about the risk of relapses and recurrences and explain what disease features and early-warning signs should be looked for;
- develop strategies, together with the patients themselves, for what they ought to do in case these features should arise.

With the patients' consent, these matters should be brought to the attention of their primary-care physicians (pediatricians and general practitioners), who are more accessible than specialists and thus tend to see the affected children and adolescents when they are in remission, rather than during an acute episode. The goal of involving primary-care physicians is to provide the patients with additional support in carrying out the strategies that were agreed upon (CCP).

The need for further research

Many questions in this area cannot be answered because of the lack of sufficiently informative comparative studies of different treatments for depressive disorders in childhood and adolescence (especially in childhood). In particular, there is a glaring lack of clinical studies in the German health-care system; there have been no studies, for example, of day hospital care or inpatient treatment, nor has there been any study with a follow-up period longer than 12 weeks. All of the recommendations of this guideline are based on the current state of scientific knowledge and may need to be fundamentally revised when an updated version of the guideline is prepared five years from now.

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Conflict of interest statement

The authors state that they have no conflict of interest.

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CLINICAL PRACTICE GUIDELINE

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eTABLE

Evidence levels and recommendation grades for treatment (Oxford Centre for Evidence-Based Medicine, [8])

Question	Step 1 Evidence level 1* ¹	Step 2 Evidence level 2* ¹	Step 3 Evidence level 3* ¹	Step 4 Evidence level 4* ¹	Step 5 Evidence level 5
What will happen if we do not offer/add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of RCT	Case-series or case-control studies, or poor quality prognostic cohort study* ²	–
Does this intervention help? (Treatment Benefits)	Systematic review of RCTs or <i>n</i> -of-1 trials	RCT or observational study with dramatic effect	Non-randomized controlled cohort / follow-up study	Case-series, case-control studies, or historically controlled studies* ²	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of RCTs or of nested case-control studies, <i>n</i> -of-1 trial with a patient of the pertinent type, or observational study with dramatic effect		Non-randomized controlled cohort / follow-up study with adequate sample size and follow-up duration		
What are the RARE harms? (Treatment Harms)	Systematic review of RCTs or <i>n</i> -of-1 trial				
Recommendation grade	A: strong recommendation ↑↑ consistent studies* ³ with evidence level 1 or 2		B: Recommendation ↑ consistent studies with evidence level 3 or 4, or extrapolations* ³ from studies with evidence level 1 or 2		0: open recommendation ↔ studies with evidence level 5, or extrapolations* ³ from studies with evidence level 3 or 4
	Clinical consensus point (CCP): Standard of treatment about which no scientifically conducted trials are feasible or desired				

RCT, randomized controlled trial: a trial with at least one intervention group and at least one control group, to which subjects are randomly assigned;

n-of-1 trial: a single-patient, randomized, controlled study.

*¹ The evidence level can be lowered because of the study's poor quality, imprecision, indirect relation to the key question, very low absolute effect strength, or inconsistency with other studies; it can be raised if the measured effect strength is high or very high.

*² Systematic reviews are, in general, preferable to individual studies.

*³ This refers to the application of study findings to situations that can differ in clinically significant ways from the situations in which the study was conducted.

↑, recommendation; ↑↑, strong recommendation; ↔, open recommendation

eBOX 1

An illustrative Medline search filter

A search for up-to-date randomized controlled trials of psychotherapy from the years 2005–2012

Module 1: population filter

(children and adolescents aged 3–18 with depressive disorders, cf. [4])

- 1 depression/ or adjustment disorders/ or depressive disorder/ or depressive disorder, major/ or dysthymic disorder/ or mood disorders/
- 2 (depress\$ or dysthym\$).mp.
- 3 1 or 2
- 4 exp adolescent/ or exp child/ or exp infant/
- 5 (child\$ or adoles\$ or teen\$ or youth\$ or infant\$ or toddler\$ or kind\$ or jugend\$ or kleinkind\$ or s\$ugling\$ or enfant\$ or jeune\$ or nourrisson\$).mp.
- 6 4 or 5
- 7 3 and 6
- 8 limit 7 to ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19–24 and 19–44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
- 9 7 not 8
- 10 limit 9 to (english or french or german)
- 11 exp Depression, Postpartum/
- 12 (postpartum\$ or perinatal\$ or antenatal\$ or postnatal\$).mp.
- 13 11 or 12
- 14 10 not 13

Module 2: method filter (here, for RCTs)

- 15 Randomized Controlled Trials as Topic/
- 16 randomized controlled trial/
- 17 Random Allocation/
- 18 Double Blind Method/
- 19 Single Blind Method/
- 20 clinical trial/
- 21 clinical trial, phase i.pt
- 22 clinical trial, phase ii.pt
- 23 clinical trial, phase iii.pt
- 24 clinical trial, phase iv.pt

- 25 controlled clinical trial.pt
- 26 randomized controlled trial.pt
- 27 multicenter study.pt
- 28 clinical trial.pt
- 29 exp Clinical Trials as topic/
- 30 or/1–15
- 31 (clinical adj trial\$).tw
- 32 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw
- 33 PLACEBOS/
- 34 placebo\$.tw
- 35 randomly allocated.tw
- 36 (allocated adj2 random\$).tw
- 37 or/17–22
- 38 16 or 23
- 39 case report.tw
- 40 letter/
- 41 historical article/
- 42 or/25–27
- 43 24 not 28

Module 3: combination of modules 1 and 2 with a topical filter (here, for psychotherapy)

- 44 14 and 43
- 45 limit 44 to yr="2005 -Current"
- 46 exp Psychotherapy/
- 47 exp Psychoanalysis/
- 48 (psychotherap* or interperson* therap* or \$ognitive* therap* or \$ognitive behavi* therap* or behavi* therap* or counsel* or problem solv* or psychoanaly* or play therap* or psychodynam* or system* therap* or famil* therap* or relaxation or supportive or psychodram* or role\$play* or transaction* or social skill* or client\$centered or verhaltenstherap* or spieltherap* or rollenspiel* or beratung* or coaching* or problemi\$se* or gespr\$chstherap* or gespr\$ch\$ps psychotherap* or gestaltttherap* or sozial* kompeten* or klientenzentrier* or therap* cognitiv\$-comportemental* or consultation*).mp.
- 49 46 or 47 or 48
- 50 45 and 49
- 51 (depress* or dysthym*).ti.
- 52 (child\$ or adoles\$ or teen\$ or youth\$ or infant\$ or toddler\$ or kind\$ or jugend\$ or kleinkind\$ or s\$ugling\$ or enfant\$ or jeune\$ or nourrisson\$ or juvenil\$).ti.
- 53 50 and 51 and 52

eBOX 2

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