Childhood and Adolescent Depression: A Review of the Past 10 Years. Part II

BORIS BIRMAHER, M.D., NEAL D. RYAN, M.D., DOUGLAS E. WILLIAMSON, B.A., DAVID A. BRENT, M.D., AND JOAN KAUFMAN, PH.D.

ABSTRACT

Objective: To review the literature of the past decade covering the assessment, treatment, and prevention of early-onset major depressive disorder (MDD) and dysthymic disorder (DD). Method: A computerized search for articles published during the past decade was made, and selected studies are presented. Results: Diagnostic systems and standardized interviews have been developed to reliably assess and diagnose early-onset MDD and DD. To date, few controlled psychotherapeutic trials, in particular cognitive-behavioral therapy (CBT), and one study using fluoxetine have been shown to be efficacious in the acute management of early-onset MDD. While studies of tricyclic antidepressants have shown no difference between medication and placebo, these studies are inconclusive because of the inclusion of small samples and other methodological issues. CBT may also be useful for the prevention of MDD. No studies have been published on maintenance treatment of MDD or the treatment of early-onset DD. Conclusions: It appears that both pharmacological and psychotherapeutic interventions have a role in the acute treatment of MDD. However, further research on the separate and combined efficacy of these treatments for the acute treatment, maintenance, and prevention of early-onset MDD and DD is needed. The impact of comorbidity and psychosocial consequences of early-onset depression also emphasize the importance of utilizing a multimodal approach to treatment. J. Am. Acad. Child Adolesc. Psychiatry, 1996, 35(12):1575–1583. Key Words: major depression, dysthymia, children, adolescents, assessment, psychopharmacology, psychotherapy, prevention.

Early-onset major depressive disorder (MDD) and dysthymic disorder (DD) are recurrent or chronic illnesses with significant morbidity and mortality requiring precise assessment, prompt treatment, and preventive interventions (Birmaher et al., 1996). This article reviews selected articles regarding the past decade of literature on the assessment, treatment, and prevention for early-onset MDD and DD.

ASSESSMENT

A crucial step before recommending any treatment for early-onset MDD or DD is a thorough evaluation of depressive symptoms, as well as symptoms of other comorbid psychiatric diagnoses, and associated psychosocial and academic problems. In addition, a medical history and examination should be conducted and laboratory tests requested if warranted. 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 standardize diagnostic procedure. In addition, several standardized interviews are available to reduce the interrater variability (e.g., Costello, 1995; Hodges, 1994; Silverman, 1994). Overall, for mood disorders for children older than 8 years, these instruments have demonstrated good interrater reliability, but test-retest reliability has not been as favorable because affective symptoms seem to be particularly unstable in this age group (Birmaher et al., 1996). Also, the agreement between parent and child in depressive symptoms is generally low. This finding is not surprising because children usually give a better account of internalizing symptoms (including suicidal ideation), whereas parents are more aware of overt behavior difficulties (e.g., Barrett et al., 1991; Walker et al., 1990). Parental information may also be influenced by a parent’s own psychopathology, underscoring the importance of obtaining information not only from the parent, but from the child and other sources (e.g., teachers). Standardized interviews are usually used for empirical studies. However, these instruments can be used also as tools for teaching residents and other mental health professionals how to ascertain a comprehensive review of psychopathology and how to ask developmentally appropriate questions of children and adolescents in a standardized manner.

Several rating scales, such as the Beck Depression Inventory (e.g., Marton et al., 1991) and the Children’s Depression Inventory (Kovacs, 1992), have also been designed to ascertain depressive symptoms in children and adolescents. Because of their low specificity, these scales are not useful for diagnosing clinical depression but can be used to screen for symptoms, to assess the severity of depressive symptoms, and to monitor clinical improvement. Finally, it is important to mention that to date, no biological tests have been shown to be useful for diagnosing MDD or DD.

TREATMENT

Psychosocial Interventions for the Acute Treatment of MDD

Several case reports and open studies have suggested the efficacy of some psychosocial interventions for the acute treatment of early-onset MDD (e.g., Clarke et al., 1992; Moreau et al., 1991; Mufson et al., 1994; Rotheram-Borus et al., 1994). Nevertheless, very few controlled psychotherapeutic investigations have been published. Preliminary findings from a large controlled study comparing 12 to 16 weeks of individual cognitive-behavioral therapy (CBT), nondirective supportive psychotherapy, and systemic behavior family therapy showed that 70% of adolescents with MDD responded to each of the three treatments, with CBT showing the most rapid reduction in self-reported depression and achieving the greatest increases in parent- and child-rated treatment credibility (Brent et al., 1995). Factors such as severity of depression, comorbid anxiety disorder, lack of support, parental psychopathology, family conflict, exposure to stressful life events, and low socioeconomic status appear to predict poorer treatment response, but further research in this area is needed (Brent et al., 1995, in press; Clarke et al., 1992; Sanford et al., 1995). The finding that comorbid anxiety predicts poorer response, together with reports showing that anxiety disorders tend to predate and persist after an episode of MDD (e.g., Kovacs et al., 1989), underscores the importance of treating not only the depressive symptoms but the comorbid anxiety disorders. A recent controlled psychotherapeutic study comparing CBT and relaxation therapies showed that brief CBT (five to eight sessions) was significantly better than relaxation training for the treatment of depressive symptoms in a clinical sample of children and adolescents with MDD and minor depression (Wood et al. in press). It is interesting that a 3- to 6-month follow-up of these patients showed no significant differences between CBT and relaxation therapies, in part because of a high relapse rate in the CBT group, and in part because patients in the relaxation group continued to recover.

The few community studies reported in samples of depressed children and adolescents have also shown the benefits of psychotherapeutic interventions. For example, in a school sample of children and adolescents with depressive symptomatology, those assigned to CBT, relaxation therapy, and self-modeling were found to fare significantly better than a waiting-list control group (Kahn et al., 1990; Reynolds and Coates, 1986). Compared with the waiting-list control condition, group CBT together with relaxation was also more effective in reducing depression both at the end of treatment and up to 2 years afterward in a group of high school students with clinical depression (Lewinsohn et al., 1990, 1994). Group problem-solving therapy was also more effective when compared with
supportive group therapy for depressed college students, both at the end of treatment and at 9-month follow-up (Lerner and Clum, 1990).

To date, only one study has offered treatment to the parents of depressed youths as part of the experimental treatment design (Lewinsohn et al., 1990). Studies assessing the effect of inclusion of parents in the treatment of depressed youths are necessary because (1) children are dependent on their parents; (2) in general, depressed youths come from families with high rates of mood disorders and a high degree of conflicts (Birmaher et al., 1996); and (3) parent psychopathology and family conflict may predict a poor outcome to treatment and increase risk for depressive recurrences (e.g., Warner et al., 1992). Psychotherapy studies comparing the efficacy of individual therapy with or without parents and siblings and examining other forms of therapy (e.g., group) in different settings (e.g., partial hospitalization, in-home services) are warranted. Well-designed psychotherapy studies will also help to answer clinical questions such as the recommended length of the treatment, the need for “booster” sessions, the “fit of treatment” (matching patients to specific therapies), the role of the therapist, and the effects of comorbid diagnoses, age, gender, race, socioeconomic status, exposure to stressful life events, and support systems. Finally, the efficacy of psychosocial treatments in prepubertal children with MDD and youths with DD needs to be studied.

Psychopharmacological Interventions for the Acute Treatment of MDD

Tricyclic Antidepressants (TCAs). Studies in Children: Open pharmacological trials in depressed children have found that 60% to 80% respond to TCAs (Geller et al., 1986; Preskorn et al., 1982; Puig-Antich et al., 1979). However, with the exception of Preskorn et al. (1987), who found a statistically significant but clinically small antidepressant effect in one of the outcome measurements, all of the controlled double-blind trials (Table 1) have reported no significant differences between placebo and TCAs (Geller et al., 1989; Hughes et al., 1990a; Kashani et al., 1984; Petti and Law, 1982; Puig-Antich et al., 1987). Furthermore, except for Geller and colleagues (1989), who found 31% response to nortriptyline and 17% to placebo in a sample of children with chronic depression, the other trials found approximately a 50% response rate to both TCAs and placebo.

Studies in Adolescents: Open psychopharmacological trials in adolescents with MDD using imipramine or nortriptyline have reported a 44% to 75% improvement (Ambrosini et al., 1994; Ryan et al., 1986; Strober et al., 1990). However, to date, double-blind trials (Table 2) have not found increased efficacy for the TCAs over placebo. Five double-blind studies comparing TCAs (amitriptyline, imipramine, and desipramine) with placebo for adolescent outpatients with MDD have reported no significant differences (Geller et al., 1990; Klein and Koplewicz, 1990; Kramer and Feigewire, 1981; Kutcher et al., 1994; Kye et al., 1996). Except for the findings of Geller and colleagues (1990), response rates to both TCAs and placebo ranged from 40% to 60%. Geller and colleagues’ study (1990) differs from other studies in that the subjects had histories of more severe and chronic depression, and only 8% responded to nortriptyline and 21% to placebo.

Taken together, these studies suggest that TCAs are no more effective than placebo for the treatment of MDD in children and adolescents. Nevertheless, these results need to be considered in light of several methodological limitations, including the following: (1) most studies consisted of a relatively small number of patients; (2) in general, most studies included patients with mild to moderate depression; (3) studies included patients with secondary depression, who may have had a higher placebo response than patients with primary depression (Hughes et al., 1990a); (4) antidepressants were generally administered for 6 to 8 weeks and may have needed to be administered for longer periods of time as evidenced by higher rates of improvement when nortriptyline was openly administered for 10 weeks (Ambrosini et al., 1994); and (5) some studies administered insufficient doses of medications (for detailed descriptions of each study, see Kye and Ryan, 1995). Compared with the vast number of studies examining the efficacy of TCAs in depressed adults (e.g., Burke and Preskorn, 1995), there have been only five double-blind controlled trials in adolescents and six in children. For example, from 1958 to 1972 alone, 85 randomized trials were performed in adults, of which 30% found no differences between TCA and placebo (Morris and Beck, 1974). In addition, compared with adult studies, the number of depressed
children and adolescents included in each study was small, resulting in decreased power to detect the efficacy of TCAs. In fact, the largest double-blind trial in depressed adolescents and children included 42 and 50 subjects, respectively, and in order to detect a 33% difference between the TCA and placebo response, a sample of approximately 120 subjects is required.

Most of the above studies reported that the placebo response in children and adolescents was 50% to 70%. In contrast, the placebo response in depressed adults has ranged from 30% to 40% (Burke and Preskorn, 1995; Morris and Beck, 1974), suggesting that children and adolescents are more likely to respond to placebo than the adult populations. Possible factors associated with the high placebo response in children and adolescents include the following: (1) the instability of affective symptoms in young populations (Birmaher et al., 1996); (2) the inclusion of patients with mild to moderate depression; (3) the lower prevalence of melancholic depression among children and adolescents (Birmaher et al., 1996); and (4) the high prevalence of comorbid conditions, particularly disruptive disorders (Hughes et al., 1990a). It is important to note that despite the fact that many children and adolescents

### TABLE 1
TCA Double-Blind Studies in Children with Major Depressive Disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Diagnostic Assessment</th>
<th>TCA</th>
<th>Dose</th>
<th>TCA Treatment Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petti &amp; Law, 1982</td>
<td>6</td>
<td>Clinical</td>
<td>IMI</td>
<td>Up to 5 mg/kg/day</td>
<td>4 weeks</td>
<td>IMI = placebo</td>
</tr>
<tr>
<td>Kashani et al., 1984</td>
<td>9</td>
<td>DSM-III</td>
<td>AMI</td>
<td>1.5 mg/kg/day</td>
<td>Crossover: each phase 4 weeks</td>
<td>AMI = placebo</td>
</tr>
<tr>
<td>Preskorn et al., 1987</td>
<td>30</td>
<td>DICA/DSM-III</td>
<td>IMI</td>
<td>Up to 5 mg/kg/day</td>
<td>6 weeks</td>
<td>IMI = placebo</td>
</tr>
<tr>
<td>Puig-Antich et al., 1987</td>
<td>38</td>
<td>K-SADS/RDC</td>
<td>AMI</td>
<td>Up to 5 mg/kg/day</td>
<td>5 weeks</td>
<td>AMI = placebo</td>
</tr>
<tr>
<td>Geller et al., 1989</td>
<td>50</td>
<td>K-SADS-RDC</td>
<td>NT</td>
<td>&quot;Fixed&quot; plasma level (80 ± 20 ng/mL)</td>
<td>8 weeks</td>
<td>NT = placebo</td>
</tr>
<tr>
<td>Hughes et al., 1990a</td>
<td>31</td>
<td>DICA/DSM-III</td>
<td>IMI</td>
<td>?</td>
<td>6 weeks</td>
<td>IMI = placebo</td>
</tr>
</tbody>
</table>

Note: TCA = tricyclic antidepressant; DICA = Diagnostic Interview for Children and Adolescents; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; RDC = Research Diagnostic Criteria; IMI = imipramine; AMI = amitriptyline; NT = nortriptyline.

### TABLE 2
TCA Double-Blind Treatments in Adolescents with Major Depressive Disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Diagnostic Assessment</th>
<th>TCA</th>
<th>Dose</th>
<th>TCA Treatment Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer &amp; Feiguine, 1981</td>
<td>20</td>
<td>?</td>
<td>AMI</td>
<td>200 mg/day</td>
<td>6 weeks</td>
<td>AMI = placebo</td>
</tr>
<tr>
<td>Geller et al., 1990</td>
<td>31</td>
<td>K-SADS/RDC</td>
<td>NT</td>
<td>&quot;Fixed&quot; plasma levels (80 ± 20 ng/mL)</td>
<td>8 weeks</td>
<td>NT = placebo</td>
</tr>
<tr>
<td>Klein &amp; Koplewicz, 1990</td>
<td>30</td>
<td>K-SADS/DSM-III-R</td>
<td>DMI</td>
<td>Up to 5 mg/kg/day</td>
<td>6 weeks</td>
<td>AMI = placebo</td>
</tr>
<tr>
<td>Kutcher et al., 1994</td>
<td>60</td>
<td>K-SADS/DSM-III-R</td>
<td>DMI</td>
<td>200 mg/day</td>
<td>6 weeks</td>
<td>DMI = placebo</td>
</tr>
<tr>
<td>Kye et al., 1996</td>
<td>31</td>
<td>K-SADS/DSM-III-R</td>
<td>AMI</td>
<td>Up to 5 mg/kg/day</td>
<td>6 weeks</td>
<td>AMI = placebo</td>
</tr>
</tbody>
</table>

Note: TCA = tricyclic antidepressant; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; RDC = Research Diagnostic Criteria; AMI = amitriptyline; NT = nortriptyline; DMI = desipramine.
respond to placebo, a follow-up study showed that placebo responders had MDD recurrences as frequently as non-placebo responders and patients who responded to nortriptyline (Geller et al., 1992).

To understand the response of children and adolescents to antidepressants, it is also important to take into account some developmental issues. For example, most of the studies cited above have used tertiary amines or noradrenergic TCAs, resulting in some greater noradrenergic effects, and in contrast to the serotoninergic and cholinergic systems, the noradrenergic system is not fully developed until early adulthood (e.g., Murrin et al., 1985; Nordberg, 1986). Moreover, children have more efficient hepatic metabolism of drugs than adults, resulting in rapid deamination of TCAs and, as a consequence, relatively less serotoninergic amines TCAs available (Clein and Riddle, 1995; Kye and Ryan, 1995). At least for the adolescents, hormonal changes that accompany puberty may also interfere with the TCA response. For example, high gonadal steroid levels may significantly inhibit the monoamine neurotransmitter function (e.g., Grenngrass and Tongue, 1974). Some phenomenological characteristics of childhood depression may also be important to understand children’s response to medications. For example, more depressed adolescents show transition into bipolar disorder than adults (Birmaher et al., 1996), and bipolar depression seems to be less responsive to TCAs (Himmelhoch et al., 1991). Also, depressed adolescents may have more atypical symptoms of depression, and these symptoms tend to improve more with monoamine oxidase inhibitors (MAOIs) than TCAs (e.g., Stewart et al., 1993).

More controlled studies in large samples of children and adolescents with MDD or DD are needed. Also, investigations comparing specific classes of antidepressants for depressed children and adolescents with different comorbid conditions (e.g., TCAs versus SSRIs for depressed children with comorbid attention-deficit hyperactivity disorder) are warranted.

Selective Serotonin Reuptake Inhibitors (SSRIs). The reports that SSRIs are efficacious for the treatment of adults with MDD (e.g., Greenberg et al., 1994), together with the findings that SSRIs have a relatively benign side effect profile, low lethality after an overdose, and easy administration (once a day), have facilitated the use of SSRIs in children and adolescents. In fact, from 1989 to 1994, SSRI prescriptions for these populations by physicians has increased fourfold (data obtained from the National Disease and Therapeutic Index, 1994). Open studies have reported 70% to 90% response to fluoxetine for the treatment of adolescents with MDD (Boulos et al., 1992; Colle et al., 1994; Jain et al., 1992). A double-blind, placebo-controlled study in a very small sample of adolescents with MDD did not find significant differences between placebo and fluoxetine (Simeon et al., 1990). However, preliminary findings of an 8-week double-blind study for the treatment of a large sample (n = 96) of children and adolescents with MDD showed a statistically significant improvement of patients taking fluoxetine (56%) over those taking placebo (33%) in one of the outcome measurements (Emslie et al., in press). The response to fluoxetine was similar in males and females, and there were no differences between children and adolescents. Despite the significant response to fluoxetine, many patients had only partial improvement, suggesting that the ideal treatment may involve variation in dose or length of treatment, or a combination of pharmacological and psychosocial treatments.

Very few studies have investigated the treatment of psychotic depression (Puig-Antich et al., 1979) or seasonal affective disorder (Mghir and Vincent, 1991), and no investigations have been reported with atypical depression and premenstrual dysphoric disorder. These subtypes of depression may require additional treatment approaches such as addition of neuroleptics or risperidone, use of light therapy, or use of MAOIs.

Plasma Levels. Except for checking for toxic levels or treatment compliance, the lack of significant correlations between antidepressant blood levels and clinical response and the large interindividual variability in plasma drug concentration at a given dose has brought into question the utility of antidepressant blood levels in depressed adolescents (Clein and Riddle, 1995; Kye and Ryan, 1995). In contrast, significant correlations between higher plasma TCA levels and clinical response have been reported in children with MDD (Geller et al., 1986; Freskorn et al., 1982; Puig-Antich et al., 1979, 1987). However, this finding needs replication using larger samples of depressed children.

Very few studies have analyzed the pharmacokinetics of antidepressants in children and adolescents (e.g., Klein and Riddle, 1995; Kye and Ryan, 1995). The metabolism, distribution, half-life, and protein binding...
of the antidepressant medications in children and adolescents appear to be different compared with adults, underlying the need to examine the developmental differences in the pharmacokinetics in early-onset depression.

Treatment of Refractory MDD

Despite the tendency for some children and adolescents to show an acute placebo response, certain subgroups of depressed children and adolescents are refractory to treatment. In adults with resistant depression, several strategies have been recommended (Thase and Rush, 1995); however, there are very few pharmacological and no psychotherapy studies of children and adolescents with treatment-refractory depression. An open study showed significant improvement of refractory depressive symptoms after augmentation of TCA treatment with lithium (Ryan et al., 1988a, b). Nevertheless, another open-label study did not replicate this finding (Strober et al., 1992). Finally, anecdotal reports have suggested that adolescents with refractory depression may respond to electroconvulsive therapy (Ghaziuddin et al., 1995; Kutcher, Strober, Birmaher, personal communications) or MAOIs (Ryan et al., 1988b).

Maintenance Treatment

MDD is a highly recurrent disorder (Birmaher et al., 1996). Furthermore, following psychopharmacological treatment or after successful psychotherapeutic treatment, MDD usually recurs (e.g., Brent et al., 1995; Geller et al., 1992; Hughes et al., 1990b; Wood et al., in press), indicating the need for psychotherapeutic and/or pharmacological maintenance treatments. Maintenance psychotherapeutic and pharmacological trials in adults with nonpsychotic, nonbipolar MDD have shown that antidepressants and mood-stabilizer medications (e.g., lithium) alone or in combination with psychotherapy can significantly reduce the occurrence of additional MDD episodes (Frank et al., 1990; Kupfer et al., 1992). Maintenance treatment has been recommended for adult depressed patients with three or more episodes and for patients with two episodes who have one or more of the following criteria: (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. Similar guidelines are needed for depressed youths.

PREVENTION

Despite the consistent reports that early-onset depression is a recurrent or chronic illness, very few investigations of this condition have addressed the prevention of relapses. In depressed adults, studies have shown that earlier treatment in the course of the illness is associated with shortened total episode duration (Kupfer et al., 1989). Furthermore, the ongoing use of psychosocial therapy and/or antidepressants has been shown to reduce relapse rates (e.g., Frank et al., 1990; Kupfer et al., 1992). Community studies of adolescents have shown that group CBT together with relaxation and group problem-solving therapy may prevent recurrences of depression for up to 9 to 24 months posttreatment (Lerner and Clum, 1990; Lewinsohn et al., 1990, 1994, respectively). A poor psychosocial outcome has been associated with recurrent depression, rather than a single episode of depression (Rao et al., 1995), underscoring the importance of developing comprehensive prevention strategies in this population.

There are no published prevention studies for children and adolescents with DD. However, as Kovacs et al. (1994) suggested, the interval between the onset of dysthymia and the first episode of MDD may provide a window of opportunity for effective prevention of continued dysthymia or the onset of a depressive episode.

Prevention of depression for children and adolescents at high risk of developing depression, such as the offspring of depressed parents (Beardslee et al., 1993), and children with depressive symptomatology but not clinical depression (e.g., Dohrenwend et al., 1980; Roberts, 1987; Weissman et al., 1992), is of prime importance. Recent studies of high school adolescents (Clarke et al., 1995) and schoolchildren (Jaycox et al., 1994) with subclinical symptoms of depression showed that cognitive interventions were effective in reducing depressive symptomatology and lowered the risk for developing depression up to 2 years after the intervention.

Finally, as part of the preventive measurements, it is crucial to educate children, adolescents, parents, teachers, and the community about early-onset depression. There is evidence that educational approaches may improve compliance and outcome in studies of adults with mood and other disorders (e.g., Haas et al., 1988; Hogarty et al., 1986). A recent psychoeducational program using an educative manual for depression showed that parents improved their knowledge and
decreased their biases about depression (Brent et al., 1993; Poling, 1994). It remains to be seen whether the increase in awareness about depression augments the number of youths or their parents seeking help earlier during their depression, greater acceptance of this disorder, and compliance with treatment.

Conclusions

Psychosocial and pharmacological treatments are vital to the acute and long-term course of MDD and dysthymia in children and adolescents, but further research is needed to fine-tune treatment strategies with an emphasis on prevention of recurrences. The high degree of comorbidity and psychosocial and academic consequences of depression also emphasize the importance of a multimodal treatment approach. The high incidence of parental mental health problems indicates the need for further research on concurrent treatment of parents and depressed youths. Also, more research is needed on the treatment of dysthymia, double depression, psychotic depression, and refractory depression. It appears that there is a role for both psychotherapeutic and psychopharmacological interventions for the treatment of early-onset depression. Based on the extant literature and our clinical experience, psychotherapy, in particular CBT, appears to be a useful initial treatment for depressed youths. Antidepressant medications seem 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 depressions that do not respond to or cannot be prevented with psychotherapy; psychotic depression; and bipolar depression. However, given the recent results by Emmslie and colleagues (in press), SSRIs may also be a good alternative initial treatment for depressed children and adolescents. Conclusive treatment recommendations can only be made after further research examining the short- and long-term efficacy of psychotherapeutic and psychopharmacological treatments, both separately and in combination.

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1582

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1582


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