Published in final edited form as:

Asian J Psychiatr. 2014 October ; 0: 13–19. doi:10.1016/j.ajp.2014.03.014.

A Naturalistic Study of Suicidal Adolescents Treated with an SSRI: Suicidal Ideation and Behavior during 3-Month Post-Hospitalization Period

Neera Ghaziuddin, MD., MRCPsych, Christopher Merchant, PhD.^{*}, Richard Dopp, MD., and Cheryl King, PhD.

University of Michigan, Ann Arbor

^{*}Northeastern Illinois University

Abstract

Objective—Describe suicidal ideation and suicide related/other emergencies (SRE), among depressed and acutely suicidal adolescents during a 3-month period following psychiatric hospitalization.

Methods—120 adolescents, who were both depressed and suicidal, were receiving an SSRI either alone or in combination with other medications, remained on a consistent medication regimen between baseline and at 3-months and their three month outcome data were available. The participants were divided into four medication groups: SSRI antidepressant only (n = 71); SSRI plus mood stabilizer (n = 17); SSRI plus antipsychotic (n = 20); and SSRI plus antipsychotic and mood stabilizer (n = 12). Standardized instruments were used.

Results—Mean age = 15.5 ± 1.3, Caucasian = 80.8%, female = 74.2%, mean CDRS-R = 61.7 ± 12.1, suicide attempt during month prior to hospitalization = 58.6%. During the 3-month post-hospitalization period: (1) There were no suicides, six participants (5%) attempted suicide and 21 (17.5 %) experienced an SRE; (2) decline in suicidal ideation and depression severity was noted; (3) SSRI plus an antipsychotic group reported the highest number of SREs; (4) Higher baseline hopelessness and aggression scores were associated with greater reduction in suicidal ideation at 3-months.

Conclusion—Declines in suicidal ideation, depression severity, and suicide attempts were noted, irrespective of psychotropic-combination received. A higher rate of SREs was associated with receiving an antipsychotic agent in combination with an SSRI. Given naturalistic design of study,

© No copyright information found. Please enter manually.

Corresponding author: Neera Ghaziuddin, Associate Professor of Psychiatry, University of Michigan, Ann Arbor, neerag@med.umich.edu, Phone: 734-764-7562, FAX: 734-936-8907.

^{*}Christopher Merchant: Assistant Professor of Psychology, Northeastern Illinois University, Chicago, C-Merchant@neiu.edu. Dr. Merchant was a doctoral student at the University of Michigan when this study was conducted.

Richard Dopp: Assistant Professor of Psychiatry, University of Michigan, Ann Arbor, dopp@med.umich.edu

Cheryl King: Professor of Psychiatry & Psychology, University of Michigan, Ann Arbor, kingca@umich.edu

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

cause-effect conclusions cannot be drawn. The lack of an objective measure to identify medication adherence is a study limitation.

Keywords

adolescents; suicide; SSRI

Introduction

The overall aim of the present study was to describe suicidal ideation and suicide- related and other emergencies during a 3-month post-hospitalization period among depressed and suicidal adolescents who were receiving SSRIs. A secondary aim of the study was to describe variability in outcome among subgroups of participants receiving SSRIs alone or in combination with antipsychotic and/or an anti-epileptic mood stabilizer medication.

The clinical significance of this study is considerable because suicidal thoughts and/or behaviors are common among depressed adolescents (Cash and Bridge 2009), and treatment of these adolescents has become increasingly challenging due to concerns of increased suicidal ideation and/or behavior in association with SSRIs. Published literature to date has addressed several important questions related to the association between suicidal ideation and/or behaviors and SSRIs. However, few studies have examined associations between SSRIs and suicidal thoughts and behaviors among adolescents who are already suicidal. Furthermore, there is scant information regarding these outcomes when SSRIs are concurrently prescribed with antipsychotics and/or anti-epileptic mood stabilizers to depressed and simultaneously suicidal adolescents.

Suicidality (completed suicide, suicide attempt, preparation towards imminent suicidal behavior, suicide ideation) is a problem intimately associated with adolescent depression and is a leading cause of death in this age group, ranked third in the United States behind accidents and malignancies (Gibbons R. D. et al. 2006). Treatment of adolescent depression has been complicated by a concern raised in 2003 regarding a possible association between suicidality and SSRIs, which was followed by a black-box warning issued in 2004 by the Food and Drug Administration (FDA). The warning states that “antidepressants increased the risk for suicidal thinking and behavior in children, adolescents, and young adults in short-term studies of major depressive disorder” <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm09273.htm>). This regulatory decision by the FDA was based on a meta-analysis of 24 trials involving over 4,500 patients, which found a greater risk of suicidality (risk ratio=1.95; 95% CI = 1.28–2.98) during the first few months of initiating antidepressant treatment (Hammad et al. 2006).

A summary of relevant publications related to this suspected association between antidepressants and suicidality is as follows: children and adolescents treated with an SSRI may experience a modest increase in suicidal ideation and behaviors- noted in a meta-analysis of 24 trials (the majority sponsored by pharmaceutical companies with the exception of the TADS multicenter trial) (Hammad et al. 2006). However, another meta-analysis of 27 trials involving adolescents with MDD, non-OCD anxiety or OCD (trials conducted between 1988 to 2006), found only a non-significant increased risk in suicidal

ideation and behaviors among those who had received an SSRI compared with placebo, irrespective of diagnosis (Bridge J. A. et al. 2007). A case-control study of Medicaid recipients who were depressed, found that children and adolescents receiving an SSRI, but not adults, are more likely to attempt suicide (OR 1.52; 95% CI) or die by suicide (OR 15.62; 95% CI). Several explanations have been offered about this association. One of these was the result of a re-analysis of randomized controlled studies of fluoxetine in youth, which found that although depressive symptoms improved following fluoxetine, suicidal thoughts or behaviors did not improve in this age group (Gibbons Robert D. et al. 2012, Gibbons R. D. et al. 2007, Nemeroff et al. 2007, Valluri et al. 2010, Valuck et al. 2004)

Another study suggested that adolescents who engage in suicidal behaviors had, in fact, not received adequate treatment with antidepressants (Dudley et al. 2010). Along similar lines, one other study found that pre-treatment patient characteristics largely accounted for increased suicidality (Kuba et al. 2011), while others have stated that the studies which formed the basis of the FDA regulatory decision were limited due to the exclusion of suicidal adolescents in clinical trials (Antonuccio 2008, Jureidini and McHenry 2009)

In addition to the concern regarding the safety of antidepressants, the FDA recently introduced a warning regarding an increased risk of suicidal thoughts and behaviors associated with several anti-epileptic drugs (AEDs). This risk involving AEDs is pertinent to psychiatrists because these agents are often prescribed as mood stabilizers. Although, this warning does not specifically involve adolescents, it adds to the concern due to the overall higher risk of suicidality among adolescents. The FDA's warning regarding AEDs was based on a review of 199 trials involving eleven different agents; four participants receiving an active agent had died by suicide. Because of concerns involving both SSRIs and AEDs, it is pertinent to examine the effect of AED-mood stabilizers on suicidal ideation and behavior and whether these agents may add to the risk of suicidality, when received in conjunction with SSRIs. This class of agents (valproate, carbamazepine, oxycarbamazepine (to name a few) is often prescribed for mood stabilization among adolescents who either do not respond to SSRIs alone, or who present with symptoms that may be responsive to these agents.

A re-examination of the suicide rates during the past decade has shown a puzzling increase with United States experiencing its largest ever year-to-year increase (14% between 2003 and 2004) since the Center for Disease Control (CDC) first started systematic collection of suicide data in 1979. Similarly, the Netherlands had experienced a dramatic increase of 49% for the same period (Gibbons R. D. et al. 2007). Further, independent researchers found that the rise in adolescent suicide rate for period 2003 to 2004 remained largely unchanged for 2005 (Bridge Jeffrey A. et al. 2008), which bolstered the initial concerns that the increased suicidality noted during 2003 to 2004 was possibly associated with a change in antidepressant-prescribing practice. However, a decline in the suicide rate in 2006 and 2007 to 6.9 per 100,000 has been reassuring. Nevertheless, longer term data are necessary to understand these fluctuations and whether the FDA warning had indeed resulted in a temporary change in clinical practice that was associated with an increased suicide rate in the US and abroad. Clearly, the pharmacotherapy of adolescent depression continues to be fraught with concerns.

Although, it is beyond the scope of this study to clarify the overall association between suicidality and SSRIs, we describe here suicide-related events (SREs) among depressed adolescents who were acutely suicidal at study entry and were receiving a SSRI during a 3-month period following a psychiatric hospitalization. Additionally, in keeping with our secondary objective, we examine variability, if any, in SRE- rates among subgroups of adolescents receiving an SSRI alone, or in combination with other psychotropic medications.

Methods

Participants and Study Design

Data were extracted from hospitalized subjects who had participated in an IRB approved psychosocial intervention study (Youth Nominated Support Team – II, funded by National Institute of Mental Health [R01 MH63881]; n = 448). The inclusion criteria for the parent study were 1) a recent suicide attempt (during the past month), or severe, unrelenting suicidal ideation, 2) ages 13–17 years, 3) parent or guardian informed consent and adolescent assent. Exclusion criteria were: 1) severe cognitive impairment and/or active psychosis, 2) direct transfer to medical unit, 3) transfer to residential placement, 4) lived > 40 miles or 1-hour driving time from hospital) (King CA et al. 2009). From this larger group recruited for the parent study, additional data were extracted for a subgroup (n = 120) that met the criteria for the present study: 1) diagnosis of any depression, based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children (definite, partially remitted or probable diagnoses for major depression, dysthymia, or depressive disorder NOS) (KSADS-PL; (Kaufman et al. 1997); 2) receiving an SSRI (either alone or in combination with other psychotropic agents, but not another type of antidepressant; i.e. tricyclic antidepressant and/or MAOI); 3) receiving a consistent medication regimen during the 3-month follow-up study period. Although, 220 participants initially met the inclusion criteria for the present study, 75 (34.1%) were excluded from the follow-up analyses because of lack of 3-month data, while 25 (11.4%) were examined separately because of changes made to their medication regimen. Reasons or the timing when the SSRI, mood stabilizer or an antipsychotic were initiated were not recorded during the data collection. Also not available were the age of onset of the depressive disorder.

The 75 participants lost to follow-up at 3 months were compared to the 145 adolescents with 3-month follow-up data. No significant differences were found between the retained and the lost-to-follow-up groups in terms of demographics, the type or the severity of psychiatric symptoms. Of the 145 adolescents for whom we had follow up data, 25 did not remain in the same medication group that they had started in. Therefore, the final group consisted of 120 who remained on a consistent treatment regimen, in addition to meeting other study related criteria.

These final 120 adolescents were grouped on the basis of other psychotropic medications received at study entry, in addition to an SSRI: SSRIs alone (SSRI; n = 71), SSRI combined with a mood stabilizer (SSRI + MS; n = 17), SSRI combined with an antipsychotic (SSRI + AP; n = 20) and SSRI combined with a mood stabilizer and an antipsychotic (SSRI + BOTH;

n = 12). Adolescents were not excluded based on their usage of ADHD medication (stimulant or non-stimulant) or a benzodiazepine.

Standardized Measures

All standardized instruments described below, except for the Services Assessment Record (SARS; (Jensen et al. 2004) and the Critical Incident Check (CIC; King C.A 2000, unpublished)), were completed at study entry. These two instruments (CIC and the SARS) were only completed at three months. Instruments that were repeated at three months included the Children's Depression Scale-Revised (Poznanski et al. 1984) and the Suicidal Ideation Questionnaire (Reynolds 1988).

The Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS-PL; Kaufman, Birmaher, Brent, & Rao, 1997): The KSADS-PL is a semi-structured clinical interview, designed to assess the presence of DSM-IV mental disorders. Interviewers were trained mental health professionals who completed 20 hours of KSADS-PL training and established inter-rater reliability with a senior diagnostician on four consecutive interviews prior to study onset.

The Children's Depression Rating Scale-Revised (CDRS-R; Poznanski & Mokros, 1996): is a semi-structured interview conducted with adolescents to assess the severity of depressive symptoms within the previous two weeks. Inter-rater reliability in the study was high (mean alpha across raters = .98).

The Beck Hopelessness Scale (BHS; Beck 1988): This is a self-report measure that has been shown to have good internal consistency (with a KR-20 coefficient of .86), strong concurrent validity (indicated by a positive correlation with depression [$r = .53$], and a negative correlation with reasons for living [$r = -.65$] among adolescent psychiatric inpatients.

The Suicidal Ideation Questionnaire-Junior (SIQ-JR; Reynolds 1988): This is a 15-item self-report questionnaire for assessing the frequency of suicidal thoughts. Higher total scores indicate higher severity of suicidal ideation. Total scores on the SIQ-JR have shown high internal consistency ($r_{\alpha} = .91$) and test-retest reliability ($r_{tt} = .91$) (Mazza and Reynolds 1999).

The Youth Self-Report (YSR; (Achenbach 1991): This is a 112-item scale that assesses a broad range of psychopathology. It has two broadband scales (internalizing and externalizing) that have demonstrated good construct validity and correlations with related self-report measures (Thurber and Hollingsworth 1992). For the sample from which these participants were selected (YST – II study), internal consistency was .89 for the internalizing scale and .86 for the externalizing. Additionally, there are eight narrowband subscales (social problems, thought problems, attention problems, withdrawn, somatic complaints, anxious/depressed, delinquent behavior, and aggressive behavior).

The Multidimensional Anxiety Scale for Children (MASC; March et al. 1997): This is a 39-item rating scale, completed by a child or an adolescent to assess a broad spectrum of

anxiety symptoms. Each item is scored on a 4-point Likert scale. The MASC has demonstrated excellent test-retest reliability, with correlation coefficients among adolescents ranging from .75 for the Perfectionism subscale to .90 for the Tense subscale (March and Sullivan 1999).

The Child and Adolescent Social and Adaptive Functioning Scale (CASAFS; Price et al. 2002) is a 24 item self-report inventory developed specifically to examine social and adaptive functioning. Findings support the scale's reliability, validity, and sensitivity to the impact of a depressive disorder. Subscales include school performance, peer relationships, family relationship, and home duties/self-care. Higher scores indicate better functioning.

The Services Assessment Record - Parent Interview (SAR; Preuss and King, unpublished) was specifically developed to assess treatment adherence during intervention and follow-up periods. Its structure and format was adapted from the Services Assessment for Children and Adolescents - Parent Interview (Jensen et al. 2004). The SARS was used to obtain information at 3-month follow-up assessment regarding medications, medication changes, psychosocial treatments, use of intensive services (e.g., psychiatric hospitalizations), and number of appointments attended for medication and/or psychosocial treatment.

The Critical Incidents Checklist (King C.A 2000, unpublished)) is a 15-item self-report measure about the presence and number of a variety of adverse events for the interval since the participant's last contact with the study team. This measure includes questions pertaining to history of abuse with responses coded as a "yes/no".

The Diagnostic Interview Schedule for Children-IV (DISC-IV; Shaffer et al. 2000) records suicide attempts in the past year and the adolescent's lifetime.

Suicide Related and other Emergency (SRE) is a composite critical incident variable, which was created for assessment at 3-month follow-up. This variable is based on a parent's or the adolescent's report about a suicide attempt, psychiatric hospitalization (for any reason), or suicide-related visit to the emergency department. This variable was created from items on the CIC and the DISC-IV. It is important to note that the YST-II intervention (parent study) was not associated with a reduction in adolescent suicide attempts (King CA et al. 2009).

Data Analyses and Results

Analyses of baseline clinical features were conducted for the 220 participants who had met the study criteria initially (regardless of 3-month outcome data or consistency of medication combination). Within this sample, the medication groups differed significantly on baseline aggressive behavior ($F [3] = 2.713, p = .046$) and baseline thought problems ($F [3] = 5.631, p = .001$) identified on YSR subscales. Participants who were prescribed SSRI + AP reported significantly greater thought problems than those prescribed SSRI alone or SSRI + MS; however, this group (SSRI + AP) did not significantly differ from SSRI + BOTH. Problems with aggressive behavior were significantly more common among those prescribed SSRI + BOTH, than among those prescribed an SSRI alone. There were no other group differences on the YSR. Additionally, there were no medication group differences for the MASC subscales, BHS, SIQ-JR, CASAFS or CDRS-R. It should be noted that these

group differences (related to thought problems or aggression) were not detected among the 120 who were further selected for the 3-month follow up analyses; this was possibly related to the smaller number of participants in each group and reduced statistical power. For the purpose of this study, this group of 120 is designated as the “consistent medication sample.”

Consistent Medication Sample

There were 120 participants who continued to be prescribed the same medication combinations during the 3-month post-hospitalization period (consistent medication groups). Chi-square and ANOVA analyses indicated no difference by medication group for any demographic variables. Among this group, the majority (90.8%) was participating in individual, family, or group therapy at baseline; with an average of 5.2 sessions between baseline and 3-month follow-up. There were no differences between the medication groups in either the proportion of adolescents in therapy or in the average number of sessions received. See Table 1 for racial/ethnic breakdown, parental income, education and psychotherapy information for the sample and by medication group.

T-test and chi-square analyses revealed no differences in age, sex, or race between the 120 (consistent medication group) adolescents and the 25 who were inconsistent (non-consistent medication group; medication changes were made at request of the patient, the family or were physician-directed). Additionally, these groups did not differ on past history of physical [$\chi^2(3) = 2.77, p = .429$] or sexual abuse [$\chi^2(3) = 6.13, p = .106$] or by psychiatric hospitalization in either parent. However, participants in the non-consistent medication group were more likely to be in families receiving public assistance (16.7% vs. 3.4%; $\chi^2(1) = 6.53, p = .011$) and scored significantly higher on MASC total scores of adolescent anxiety ($t(142) = -2.32, p = .022$). The mean MASC score for the non-consistent group was 55.2 compared with 45.7 for the consistent group. There were no other differences on any other measures of psychopathology (SIQ-JR, CDRS-R, BHS and YSR-INT, YSR-EXT). Further, there were no differences between the consistent and non-consistent groups in terms of the presence of SREs (attempts or hospitalizations) at the three-month time-point.

Differences within Consistent-Medication Groups

Table 2 presents baseline clinical features for the entire consistent-medication sample, including past history of suicide attempts, and features for each medication group within this larger group. No significant group differences were found in baseline clinical features or suicide attempt history. Table 3 presents co-morbid diagnoses for the overall consistent medication group and for each medication sub-group. Specifically, we report on the presence of any anxiety disorder, PTSD or acute stress disorder, any disruptive behavior disorder, and any substance use disorder. Chi-square analyses revealed no differences in the presentation of comorbid diagnoses between the medication groups.

3-month critical incidents and outcomes

Table 4 presents descriptive statistics for Suicide Related Emergencies (SREs), 3-month SIQ-JR scores, and the 3-month *change* in SIQ-JR scores for each of the consistent medication sub groups and the overall group. For the overall group and within each group, there was a decline in the mean 3-month SIQ-JR scores relative to at study entry (SIQ-Jr for

overall group = 47.15 ± 20.04 and post SIQ-Jr at 3 months for overall group = 21.75 ± 16.25 ; see tables 2 and 4 for details). Similarly suicide attempts reported by the entire group during the month prior to study entry declined from 58.6% to 5 % reported at 3 month follow up (Tables 2 and 4). Chi-squared analyses revealed significant differences between medication groups in the number of adolescent or parent reported psychiatric hospitalizations ($\chi^2 [3] = 16.41, p = .001$) and the number of overall suicide related emergencies ($\chi^2 [3] = 10.32, p = .016$). A series of 2×2 Chi-square tests were conducted post-hoc to determine the specific between-group differences. All medication augmentation groups (SSRI + MS, SSRI + NP, SSRI + BOTH) reported significantly elevated likelihood of a psychiatric hospitalization compared with the group receiving an SSRI alone, (17.6% vs. 1.4% for the mood stabilizer group, $\chi^2 [1] = 8.34, p = .004$; 30.0% vs. 1.4% for the antipsychotic group, $\chi^2 [1] = 17.97, p = .000$; 16.7% vs. 1.4% for the group on BOTH, $\chi^2 [1] = 6.86, p = .009$). Additionally, those receiving an SSRI with an antipsychotic were more likely to report an SRE than those receiving an SSRI alone (40.0% vs. 9.9%, $\chi^2 [1] = 10.30, p = .001$). There were no other statistically significant differences between the groups in terms of suicide related emergencies, hospitalizations, or suicide attempts.

Multiple linear regression was used to identify which variables had influenced the suicidality related outcomes among the medication groups. The dependent variable in these analyses was change in SIQ-JR from baseline to three months (a negative change value for an individual indicated a decrease in SIQ-JR score). Covariates were scores on measures that differed between medication groups at baseline and scores on measures with either conceptual or empirical association with suicidality. The covariates for the test of suicidal ideation change were medication group, YSR aggression, YSR thought problems, hopelessness, and baseline report of a suicide attempt. The overall model ($F [5,117] = 3.27, p < .01$) accounted for 12.7% of the variance in change scores. However, only two predictors individually accounted for significant variance in change scores. Higher baseline hopelessness and aggression scores were associated with greater reduction in suicidal ideation at 3-months (hopelessness: $b = -1.13, p < .001$; aggressive behavior: $b = -0.67, p = .003$).

Discussion

The main findings of the present study are: 1) adolescents reported a decline in suicidal ideation and suicidal behaviors during a 3-month post-hospitalization period; 2) Decrease in suicidal ideation at 3 month follow up, irrespective of medication group, was associated with higher baseline hopelessness and aggression; 3) statistically higher number of psychiatric hospitalizations were observed in groups SSRI + MS and SSRI + BOTH, relative to SSRI alone group; 4) and statistically higher number of suicide related emergencies were found in group SSRI + AP, relative to SSRI alone group. Based on these data, although we cannot shed light on the FDA black box warning, we concluded that suicidality was not exacerbated during treatment with an SSRI in a group of adolescents who were simultaneously depressed and acutely suicidal. Increased suicidal related outcomes noted in those who received combination medication, in particular those who received an antipsychotic agent in conjunction with an SSRI, most likely suggests a greater illness severity at baseline. Our findings also underscore a concern that has been raised that it is important to include clinical

and treatment variables, or their interaction, which are often excluded from the assessment of suicide related outcomes (Brent 2009). A major strength of the present study is that depressed and simultaneously suicidal adolescents, who are often excluded from clinical trials, but frequently present in “real life” clinic settings, were included.

Decline in suicide attempts reported at 3-month follow up relative to study entry should be viewed in context of the study design. Because our sample is comprised of adolescents who were psychiatrically hospitalized with suicide risk concerns, all medication groups include high percentages of adolescents who made suicide attempts in the past month (ranging from 45.5% to 63.1%). As has been shown in multiple published follow-up studies of suicidal and psychiatrically hospitalized adolescents during the immediate post-hospitalization period, the percentage of adolescents who report suicide attempts declines during this period. Furthermore, given our relatively small group sizes (e.g., $n = 20$ for AP), a suicide attempt rate of 10% at follow-up for this group was associated with too few participants for meaningful data analyses.

The primary goal of the present study was to describe 3-month post-hospitalization suicidal ideation and SREs (suicide attempts and other suicide related visits to the psychiatric emergency department, and admission to a psychiatric unit for any reason) among psychiatrically hospitalized adolescents who were diagnosed with depression and were suicidal at the time of study enrollment, and were treated with an SSRI, either alone or in combination with other medications. Due to the design used, these adolescents had experienced an exacerbation in symptom-severity and concerns for their safety that had resulted in hospitalization immediately prior to participation in the study. Comparison of medication based groups at 3-month follow-up allowed us to examine clinically meaningful outcomes, although the interpretation of our findings is clearly limited by the naturalistic assignment to medication groups and by the absence of an SSRI-free control group. Conversely, the advantage of the present design is that outcomes are examined among participants in a “real life” clinical situation, where SSRIs and antipsychotics and/or mood stabilizers are frequently prescribed based on clinician-preference, although the data are sparse to support the use of antipsychotics for non- psychotic conditions in this age group (Verdoux et al. 2010).

A supplemental analysis of all participants ($n = 220$), who had met the initial study-criteria, had found higher baseline thought problems in participants who belonged to the group that was receiving SSRI with an antipsychotic agent (SSRI + AP). Similarly, the group receiving an SSRI in conjunction with a mood stabilizer and an antipsychotic agent (SSRI + BOTH) had higher scores for aggressive behavior. It should be noted that presence of active psychotic symptoms was an exclusion criteria for the parent study and the YSR thought problem subscale score is not considered indicative of psychotic symptoms. Furthermore, these differences (higher thought problems or aggression) were not apparent when the analyses were limited to the final group ($n=120$) who had remained on a consistent medication regimen at 3-month follow-up. Although, the implications of these associations- baseline “thought disturbance” and/or aggression with medications received- are unclear, it is possible that certain symptoms are more likely to raise concern, resulting in treatment with combinations, versus an SSRI alone.

It is noteworthy that antipsychotics and mood stabilizers are generally not permitted during controlled antidepressant trials. Therefore, the higher suicidal ideation and behaviors reported in children and adolescents during clinical trials maybe due to the absence of these agents (mood stabilizers and antipsychotics) for patients who may, in fact, suffer from early mixed states (patients with predominant anxiety, agitation, hostility or impulsivity), rather than a true unipolar depression (Rihmer and Akiskal 2006). We hypothesize, that the naturalistically prescribed medications during the present study may have provided pharmacological protection to our participants, which may otherwise be lacking during controlled clinical trials. Based on these data, we are unable to conclude, however, which patients may derive the most benefit from these additional agents.

Another finding of this study is that the majority of participants (55%) had continued to receive a consistent medication regimen at 3-months post-hospitalization. We had also noted that changes in medication regimen were associated with economic disadvantage (indicated by receiving public assistance) or higher anxiety at study entry. Although, no definitive conclusions can be drawn, it is possible that higher anxiety endorsed by the adolescent and/or certain parent-characteristics may more likely result in medication-changes. For instance, these factors (higher anxiety or greater economic disadvantage) may also be associated with reporting a greater number of side-effects or dissatisfaction with the treatment, thus resulting in more frequent changes in the medication regimen.

Study limitations are the absence of a control group and lack of randomization of pharmacotherapy, prior pharmacotherapy or the timing and the reason why these medications were initiated are unknown, lack of information about past history of psychotic symptoms and whether these symptoms may have resulted in the addition of an antipsychotic agent, the analyses did not control for the duration or the type of psychotherapy, the effect of other medications such as benzodiazepines or stimulants could not be determined, a predominantly Caucasian subject group did not permit us to generalize our findings to other racial groups and, finally, we did not use any objective measures for estimating medication adherence (such as serum levels or a pill count).

In summary, we conclude that suicidal thoughts and suicidal behavior among depressed and suicidal adolescents who are receiving an SSRI, either alone or combined with another agent, are not likely to be exacerbated during treatment with these agents. Furthermore, subtle clinical variables at baseline may have a greater value in predicting suicidality during treatment. To fully understand these associations, it is essential that future clinical trials should include severely depressed and simultaneously suicidal adolescents. It may also be necessary to permit medication combinations to further understand which patients would most benefit from these regimens and the effect of this practice in clinical setting.

Acknowledgments

Grant support: NIMH; R01 MH63881, NIMH: K24 MH077705

References

- Achenbach, TM. University of Vermont DoP. Integrative guide for the 1991 CBCL/ 4–18, YSR and TRF profiles. Burlington, VT: 1991.
- Antonuccio D. Treating depressed children with antidepressants: more harm than benefit? *Journal of Clinical Psychology in Medical Settings*. 2008; 15:92–97. [PubMed: 19104973]
- Beck, AT. Beck Hopelessness Scale. The Psychological Corporation; 1988.
- Brent D, Emslie GJ, Clarke GN. Predictors of spontaneous and systematically assessed suicidal adverse events in the treatment of SSRI-resistant depression in adolescents (TORDIA) study. *Am J Psychiatry*. 2009; 166:418–426. [PubMed: 19223438]
- Bridge JA, Greenhouse JB, Weldon AH, Campo JV, Kelleher KJ. Suicide trends among youths aged 10 to 19 years in the United States, 1996–2005. *Jama*. 2008; 300:1025–1026. [PubMed: 18768413]
- Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *Jama*. 2007; 297:1683. [PubMed: 17440145]
- Cash SJ, Bridge JA. Epidemiology of youth suicide and suicidal behavior. Current opinion in pediatrics. 2009; 21:613–619. [PubMed: 19644372]
- Dudley M, Goldney R, Hadzi-Pavlovic D. Are adolescents dying by suicide taking SSRI antidepressants? A review of observational studies. *Australasian Psychiatry*. 2010; 18:242–245. [PubMed: 20482427]
- Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. *American Journal of Psychiatry*. 2006; 163:1898. [PubMed: 17074941]
- Gibbons RD, Brown CH, Hur K, Davis J, Mann JJ. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. *Archives of General Psychiatry*. 2012; 69:580–587. [PubMed: 22309973]
- Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, Herings RM, Mann JJ. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *American Journal of Psychiatry*. 2007; 164:1356. [PubMed: 17728420]
- Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Archives of General Psychiatry*. 2006; 63:332. [PubMed: 16520440]
- Jensen P, Hoagwood K, Roper M, Arnold L, Odbert C, Crowe M. The services for Children and Adolescent-Parent Interview: Development and performance characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2004; 43:1334–1344. [PubMed: 15502592]
- Jureidini JN, McHenry LB. Key opinion leaders and paediatric antidepressant overprescribing. *Psychotherapy & Psychosomatics*. 2009; 78:197–201. [PubMed: 19401619]
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. see comment. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997; 36:980. [PubMed: 9204677]
- King, CA. Unpublished measure. Department of Psychiatry, University of Michigan; 2000. Critical Events Checklist. (unpublished)
- King CA, Klaus N, Kramer A, Venkataraman S, Quinlan P, Gillespie B. The Youth-Nominated Support Team-Version II for suicidal adolescents: A randomized controlled intervention trial. *Journal of Consulting & Clinical Psychology*. 2009; 77:880–893. [PubMed: 19803568]
- Kuba T, Yakushi T, Fukuhara H, Nakamoto Y, Singeo ST Jr, Tanaka O, Kondo T. Suicide-related events among child and adolescent patients during short-term antidepressant therapy. *Psychiatry & Clinical Neurosciences*. 2011; 65:239–245. [PubMed: 21507130]
- March JS, Sullivan K. Test-retest reliability of the Multidimensional Anxiety Scale for Children. *Journal of Anxiety Disorders*. 1999; 13:349–358. [PubMed: 10504106]

- March JS, Parker JD, Sullivan K, Stallings P, Conners CK. The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997; 36:554–565. [PubMed: 9100431]
- Mazza JJ, Reynolds WM. Exposure to violence in young inner-city adolescents: relationships with suicidal ideation, depression, and PTSD symptomatology. *Journal of Abnormal Child Psychology*. 1999; 27:203–213. [PubMed: 10438186]
- Nemeroff CB, Kalali A, Keller MB, Charney DS, Lenderts SE, Cascade EF, Stephenson H, Schatzberg AF. Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States. *Archives of General Psychiatry*. 2007; 64:466. [PubMed: 17404123]
- Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary studies of the reliability and validity of the children's depression rating scale. *Journal of the American Academy of Child Psychiatry*. 1984; 23:191. [PubMed: 6715741]
- Price CS, Spence SH, Sheffield J, Donovan C. The development and psychometric properties of a measure of social and adaptive functioning for children and adolescents. *Journal of Clinical Child & Adolescent Psychology*. 2002; 31:111–122. [PubMed: 11845643]
- Reynolds, WM., editor. *Suicidal Ideation Questionnaire: Professional Manual*. Odessa, FL: Psychological Assessment Resources; 1988.
- Rihmer Z, Akiskal H. Do antidepressants (h)reat(en) depressives? Toward a clinically judicious formulation of the antidepressant-suicidality FDA advisory in light of declining national suicide statistics from many countries. *Journal of affective disorders*. 2006; 94:3. [PubMed: 16712945]
- Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2000; 39:28–38. [PubMed: 10638065]
- Thurber S, Hollingsworth D. Validity of the Achenbach and Edelbrock Youth Self-Report with hospitalized adolescents. *Journal of Clinical Child & Adolescent Psychology*. 1992; 21:249–254.
- Valluri S, Zito JM, Safer DJ, Zuckerman IH, Mullins CD, Korelitz JJ. Impact of the 2004 Food and Drug Administration pediatric suicidality warning on antidepressant and psychotherapy treatment for new-onset depression. *Medical Care*. 2010; 48:947–954. [PubMed: 20856141]
- Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. *CNS Drugs*. 2004; 18:1119–1132. [PubMed: 15581382]
- Verdoux H, Tournier M, Begaud B. Antipsychotic prescribing trends: a review of pharmaco-epidemiological studies. *Acta Psychiatrica Scandinavica*. 2010; 121:4–10. [PubMed: 20059452]

Table 1

Demographic characteristics of sample; overall and by medication group

	Overall n = 120	SSRI n = 71	MS n = 17	AP n = 20	BOTH n = 12
Sex (% female)	74.2	74.6	82.4	60.0	83.3
Race (%)					
White (non-Hispanic)	80.8	78.9	76.5	85.0	91.7
Black (non-Hispanic)	5.0	5.6	11.8	0.0	0.0
Other (non-Hispanic)	7.5	9.9	5.9	5.0	8.3
Hispanic	5.8	5.6	5.9	10.0	0.0
Age (Mean (SD))	15.51(1.26)	15.60(1.08)	15.72(1.58)	15.12(1.62)	15.30(1.06)
Income (%)					
<\$40,000	17.9	23.0	11.7	15.8	0.0
\$40–\$80,000	35.7	36.9	35.3	31.6	36.4
>\$80,000	46.4	40.0	52.9	52.7	63.6
Family on public assistance? (%yes)	3.4	4.3	0.0	5.0	0.0
Youth in individual, group, or family therapy? (% yes [mean number of sessions])	95.4(4.77)	93.8(4.35)	88.2(6.53)	90.0(4.59)	90.9(4.91)

Notes: SSRI = SSRI alone, MS = SSRI + mood stabilizer, AP = SSRI + antipsychotic, BOTH = SSRI + mood stabilizer and antipsychotic.

Table 2
Baseline Psychopathology Variables for Consistent Medication Sample: Overall and by Group

	Overall n = 120 Mean (SD)	SSRI alone n = 71 Mean (SD)	SSRI + MS n = 17 Mean (SD)	SSRI + AP n = 20 Mean (SD)	SSRI+ BOTH n = 12 Mean (SD)
SIQ Jr.	47.15 (20.04)	46.65 (21.10)	44.53 (15.32)	50.65 (20.18)	48.00 (20.78)
CDRS-R	61.70 (12.08)	62.08 (12.62)	58.41 (10.83)	62.35 (12.08)	63.00 (11.10)
MASC	45.65 (18.87)	45.04 (18.76)	42.06 (17.34)	48.45 (21.97)	49.58 (16.95)
BHS	9.19 (5.75)	9.30 (5.69)	6.53 (5.63)	10.65 (5.27)	9.92 (9.46)
YSR Internalizing	28.30 (10.30)	27.88 (10.87)	26.12 (9.92)	31.15 (9.16)	29.00 (9.32)
YSR Thought Disruption	4.14 (3.12)	3.84 (3.13)	3.53 (2.81)	5.65 (3.17)	4.25 (2.99)
YSR Externalizing	19.78 (9.31)	18.63 (9.20)	19.76 (10.69)	21.65 (9.43)	23.42 (7.03)
YSR Aggression Problems	12.92 (6.49)	11.94 (6.13)	13.29 (8.05)	14.35 (7.03)	15.75 (4.29)
Has the youth attempted suicide in the past month? (% yes)	58.6	63.1	58.8	50.0	45.5
Suicide Attempts – Lifetime					
No Attempt (%)	25.8	25.4	17.6	40.0	16.7
Single Attempt (%)	35.0	38.0	35.3	20.0	41.7
Multiple Attempts (%)	39.2	36.6	47.1	40.0	41.7

Notes: SSRI = SSRI alone, MS = SSRI + mood stabilizer, AP = SSRI + mood stabilizer and a neuroleptic, BOTH = SSRI + antipsychotic, BOTH = SSRI + mood stabilizer and a neuroleptic; suicide attempt questions are based on child report on the DISC.

Table 3
Comorbid Diagnoses for Consistent Medication Sample: Overall and by Medication Group

	Overall n = 120	SSRI alone n = 71	SSRI + MS n = 17	SSRI + AP n = 20	SSRI+ BOTH n = 12
Presence of any anxiety disorder [†]	27.5	26.8	23.5	30.0	33.3
Presence of PTSD or Acute Stress Disorder	25.0	21.1	41.2	25.0	25.0
Presence of any disruptive behavior disorder ^{††}	37.5	35.2	29.4	60.0	25.0
Presence of any substance use disorder ^{†††}	16.7	18.3	17.6	5.0	25.0

Notes: Percentages presented are definite, probable, or partially remitted presence of diagnosis, all diagnoses are based on K-SADD interview,

[†] Any anxiety disorder excludes PTSD and Acute Stress Disorder; includes Separation Anxiety, Panic Disorder, Avoidant Disorder, Simple Phobia, Social Phobia, Agoraphobia, Generalized Anxiety Disorder, and Obsessive-Compulsive Disorder;

^{††} Includes Attention Deficit/Hyperactivity Disorder, Conduct Disorder, or Oppositional Defiant Disorder,

^{†††} Includes Alcohol and other substances; abuse and dependence.

Table 4

Three-month Outcome

	3-month analysis by group				
	SSRI	MS	AP	BOTH	Overall
Youth or parent reported attempt (% yes)	5.6	0.0	10.0	0.0	5.0
Youth or parent reported psychiatric hospitalization (% yes)	1.4	17.6*	30.0†	16.7*	10.0
SRE: Youth or parent reported suicide-related emergency (% yes)	9.9	23.5	40.0**	16.7	17.5
3 month SIQ-Jr. total score [Mean (SD)]	22.16 (17.21)	19.29 (7.78)	22.35 (17.39)	22.17 (18.74)	21.78 (16.25)
3 month SIQ-Jr. change score [Mean (SD)]	-24.66 (23.85)	-25.24 (16.82)	-28.30 (17.35)	-25.83 (19.94)	-25.47 (21.41)

Notes: SSRI = SSRI + mood stabilizer, AP = SSRI + mood stabilizer and an antipsychotic, BOTH = SSRI + mood stabilizer and an antipsychotic, suicide attempt, hospitalization, and emergency items taken from the CIC and DISC; negative SIQ-Jr. change score indicates a decrease in suicidal ideation

* significantly different from SSRI alone ($p < .01$),

** significantly different from SSRI alone ($p < .001$).