Subtle Psychological Side Effects:

Documentation, Description, and Treatment Implications of Subjective Experiences of Selective Serotonin Reuptake Inhibitors Taken for Depression

by

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Abstract

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Psychological side effects may affect patients' willingness to continue or return to SSRI treatment, and may be one reason for client dissatisfaction with medication. The goal of this study was to document the existence of a range of psychological side effects associated with SSRIs taken for depression and to determine their relationship to patients' decisions to stop treatment, and attitudes toward taking SSRIs again. ***Methods:*** We conducted 161 semi-structured telephone interviews of adults who had completed a course of treatment for depression with one of the SSRIs. We elicited information about drug effects on symptoms, physical side effects, unwanted psychological effects, reasons for quitting and willingness to return to the same treatment in case of future depression. We identified 29 categories of unwanted psychological effects and analyzed data in terms of Responders and Non-Responders, the former split into Renewers and Non-Renewers. ***Results:*** Contrary to expectations, Non-Renewers and Non-Responders did not differ in

the number of SEs experienced, and Non-Responders experienced significantly more unwanted psychological effects than either Renewers or Non-Renewers, $t(121) = 2.818$, $p < .01$. Twenty-seven percent of the sample cited psychological side effects and 27% cited physical side effects as primary reason for quitting SSRI treatment. Non-Responders cited psychological side effects rather than non-response as their primary reason for quitting, and Non-Renewers cited physical more than psychological side effects. ***Conclusion:*** Psychological side effects might well be included in measures and discussions of side effects, even though they present no known physical danger to the patient. ***Discussion:*** Unwanted psychological effects reported by our participants included problems with empathy, sociability, irritability, and creativity. These are interpreted as supporting a contextualist or developmental view of psychopathology. A thoroughly contextualized approach to treatment is therefore recommended.

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Acknowledgments

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Chapter 1: Reasons for Quitting SSRIs:

Paradoxical Psychological Side Effects and Patient Satisfaction

Introduction

There is a notable percentage of unexplained discontinuance of SSRI treatment for depression. Reasons for stopping antidepressant medication both in clinical trials and in general practice include side effects, attitudes to drugs and problems with patient-doctor communication (Basco & Rush, 1995; Johnson, 1981; Lin et al., 1995). A meta-analysis of published clinical trials of four to eight weeks duration compared total discontinuation rates of SSRIs and tricyclic antidepressants (TCAs) (Anderson & Tomenson, 1995). Although the total discontinuation rate was 10% lower with SSRIs than with TCAs over this time period (30% vs. 33% of all subjects), and the dropout rate due to side effects was 25% lower (15% vs. 20% of all subjects), there was no significant difference between drug classes in the dropout rates for treatment failure (that is, no improvement in symptoms—in about 7% of all subjects) (Hotopf, Hardy, & Lewis, 1997).

If 45-55% of dropouts are due to side effects when both SSRIs and TCAs are considered, and about 20-24% of dropouts are due to treatment failure (symptoms did not improve) in clinical trials, this still leaves 20-35% of dropouts not accounted for—about 8-10% of the total sample. It may be argued that dropout rates in clinical trials are not relevant to real world situations because research studies are stringent about requirements for continuation and present a different context for the patient. However the total dropout

rates are thought to be comparable to results in general practice, where rates of 30% to 70% have been reported by six weeks, some 30-40% of these being due to side effects (Hotopf, Hardy, & Lewis, 1997). What might account for the other 60-70%?

Side effects are the most common reason for discontinuation of all types of antidepressant (Basco & Rush, 1995; Johnson, 1981), and may be a deterrent to medication adherence even when symptoms of depression are ameliorated. Alternatively, if a patient is satisfied with what the medication is doing, s/he may be more able to tolerate side effects even if they do occur (Settle, 1992). Furthermore, a medication's perceived effectiveness when patients experience it under controlled conditions may be quite different from various effects reported in a representative group of patients experiencing it under real-world conditions of variable diagnosis, dosage, course of treatment, and adherence (Engstrom, 1991).

During the screening process for a study of psychotherapy for depression (Kohlenberg, 1997-2000), some patients reported that they had either stopped taking their SSRI or wished to discontinue it even though their symptoms were improving. They were not primarily concerned with the known physical side effects that are listed in the drug description or clinical trial literature, but seemed instead to be concerned with more subtle psychological side effects. We undertook this study to try to unravel the paradox: Why would patients want to discontinue treatment that was successfully addressing their symptoms? We suspected that psychological side effects—as distinct from physical side effects—may affect patients' willingness to continue, and that this may be one little-documented reason for client dissatisfaction with medication.

Evidence of unwanted psychological effects included such statements as:

"I couldn't cry on Prozac when my father died." "I was smiling, but it wasn't me," "It turned me into this kind of really productive, uncaring sort of robot." "Nothing really touched me anymore." "I was on an even keel but things didn't feel real." "I couldn't feel my feelings." "I couldn't do my art, just couldn't get into that creative place. I debated going off and being depressed, just so I could paint again."

Physical side effects that commonly lead to discontinuance of antidepressants (both TCAs and SSRIs) include nausea, diarrhea, constipation, insomnia, somnolence, tremor, dizziness, agitation, headache, dry mouth, sweating, and sexual dysfunction (Borg & Brodin, 1996). Subtler cognitive effects of antidepressants that have been reported in the literature include problems with memory, concentration and coordination, anhedonia, apathy and indifference (Baldessarini & Marsh, 1990; Glenmullen, 2000; Hoehn-Saric, Lipsey, & McLeod, 1990; Settle, 1992, 1998). These overlap somewhat with the phenomena we were interested in investigating. However definitions or operationalizations of these existing constructs differ (Hoehn-Saric, Lipsey, & McLeod, 1990; Levy et al., 1998; Lingjaerde, Ahlfors, Bech, Dencker, & Elgen, 1987; Marin, 1990a,b; Marin, Fogel, Hawkins, Duffy, & Krupp, 1995), and only partially describe the phenomena of interest to us. These subtler cognitive side effects may have been included in the "uncooperativeness" referred to in a meta-analytic article documenting a higher discontinuation rate for fluoxetine than for nortriptyline (Nelson, 1994). Because these events are not physically dangerous, we speculate that prescribers may be tempted to dismiss significant subjective experiences if they are reported, even though they may affect the patient's willingness to continue treatment.

It may be that patients are less willing to tolerate physical side effects if the

intended psychological effects are for some reason not satisfactory. After all, people are willing to put up with the discomfort and inconvenience of, for example, eyeglasses or insulin shots because the intervention has a desired effect that is important to the patient. Subjective response has been suggested as a predictor of outcome in pharmacotherapy for schizophrenia (Hogan & Awad, 1992; Hogan, Awad, & Eastwood, 1983; Van Putten & May, 1978; Van Putten, May, Marder, & Wittman, 1981), and there may be similar relationships between subjective experience, compliance and outcome in pharmacotherapy (particularly SSRIs) for depression. The current study sought to discover a little more about the relationship of symptom amelioration, side effects (physical and psychological) and patient satisfaction with SSRI treatment, particularly as it affects continuation of treatment. Inasmuch as consumer satisfaction is a factor in analyses of services (Nelson, 1994; Steiber & Krowinski, 1990), we believe that the results of this study will be of interest and use to the healing professions in the therapeutic decision-making process.

The primary goal of this study was to document the existence of a range of psychological side effects associated with SSRIs taken for depression and to determine their relationship to patient satisfaction, that is, their decisions to stop taking SSRIs and attitudes toward taking them again in the future. We hypothesized that patients who terminated SSRI treatment in spite of symptom amelioration (Non-Renewers) would endorse unwanted psychological effects more than those who terminated because symptoms were not addressed (Non-Responders) or those who were untroubled by side effects and were satisfied with the treatment (Renewers). To our knowledge, no previous study had addressed this issue.

Method

Participants

We posted flyers and placed advertisements in newspapers in the Seattle, WA area, seeking participants between the ages of 21 and 60 who had completed a course of treatment for depression with one of the SSRIs. The advertisement invited callers to "tell us about your antidepressant experiences" whether they thought the medication "was great" or "not worth the trouble," to "help us find out more about the pros and cons of antidepressant medications," and promised a "confidential telephone survey recorded for accuracy" with "anonymity an option."

Participants were 29 males and 132 females ranging in age from 22 to 60 years (mean 42.9, SD 9.2). The uneven proportion of males reflects the greater prevalence of depression in females, though if the study were repeated, more males would be sought specifically in order to bring the proportion of males up from 18% to 33%. For purposes of analysis, participants were divided into two groups: those for whom the medication worked (addressed their symptoms, n = 92) and those for whom it did not work (n = 69). There were no significant demographic differences between these groups. Callers who were taking multiple psychotropic medications or who had confounding physical or psychiatric conditions were excluded from the analysis.

We derived the "addressed symptoms" variable from the depression symptom section of the Psychological Side Effects Questionnaire (PSEQ), described below. This section was a detailed diagnostic inquiry into DSM-IV (American Psychiatric Association, 1994) depression symptoms experienced by the subject prior to being prescribed the antidepressant, and the perceived effect of the drug on each symptom. For

each symptom, the interviewer scored drug effect on a verbally anchored scale of 1 (markedly worse) to 6 (better than ever/unusually good). The score of "6" allowed us to trace manic reactions. Not all symptoms in the DSM-IV symptom list could be scored 6 (for example, suicidal ideation only reached 5, "no thoughts of death or suicide at all"). The variable "addressed" was calculated for each subject as follows:

$$\left[\frac{\sum items}{5(\#/items)}\right] \times 5 = \text{"addressed"}$$

This yielded a single score from 1 (much worse) to 5 (completely asymptomatic) to indicate objectively whether the drug worked or not. Scores above 5 indicated hypomanic or manic reactions. The mean post-SSRI score for the total sample was 3.6 (SD 1.1). We used 3.6 for a conservative cutpoint to indicate objectively whether the drug worked or not.

Procedure

Subjects called a dedicated phone line, and the interviewer explained the nature of the research. If the time was convenient for the subject, the interviewer proceeded to read an oral consent script approved by the University of Washington's Human Subjects Review Board. Subjects were asked permission to record the interview, and were told that the audiotapes would be kept indefinitely for research purposes with all identifying information kept separately. Two subjects who refused to be recorded were still interviewed after they gave consent, and the information was written down as completely as possible by the interviewer. Interviews lasted between 25 and 60 minutes, depending on the complexity of the caller's experiences.

The PSEQ study interview consisted of six sections: 1) demographics, including a brief account of the course of SSRI treatment; 2) semi-structured inquiry into unwanted psychological effects (UΨE or "UPSEs"); 3) diagnostic inquiry into (DSM-IV) depression symptoms prior to being prescribed the antidepressant, and the effect of the drug on each symptom, using verbally anchored Likert-type scaling; 4) semi-structured inquiry into unwanted physical side effects (SEs); 5) questions about education and instructions received about the medication regime (Lin et al., 1995); and 6) inquiry into a maximum of three main reasons for quitting the medication, plus an open-ended miscellaneous question to elicit additional information.

In the Unwanted Psychological Effects portion of the PSEQ, an opening question set the stage for specific probes: "People sometimes find that antidepressants affect their memory, their creativity, their feelings, how they relate to others, and even their personality. Did anything like that happen to you?" The interviewer then probed carefully to determine whether each experience being reported began after starting the SSRI, in which case it could be attributed to the drug's action, or whether the experience began before being prescribed medication, so it would properly be attributed to the depressed state or to other circumstances of the caller. Additionally, the interviewer asked whether the respondent thought this response (e.g., irritability) was appropriate to the situation, and whether or not s/he liked the effect if it was considered to be due to the drug. Every effort was made not to bias responses. Hence if a respondent felt that her/his memory, creativity, ability to relate to others, etc. had been enhanced due to the drug, this response was recorded and the same probes for detail were done as for a negative report.

The 29 items for the Unwanted Psychological Effects (UPSE) part of the PSEQ (see Table 1) were generated through an iterative process of content analysis. Each item, designed to be coded categorically as either present or absent, was then defined in a coding manual. These items are coded categorically as either present or absent. A number of UPSEs (marked with asterisks in Table 1) are paradoxical: effects that at face value might seem desirable in the context of major depression were experienced as negative—and vice versa. Sometimes this was a matter of degree, as for instance with the inability to cry. To one who had been crying too much prior to medication, stopping is a relief—on the other hand, in a context where tears would be appropriate (such as a death in the family), the inability to cry is reported as a problem. If the drug had stopped only the excesses of crying, while allowing one to cry when appropriate, patients might not have complained, since their behavior would then fit the shifts in context as needed. We called such effects "mismatches." Many experienced narrowed range of affect as negative. Though narrowing is positive for those who had been experiencing the darkest depths of depressed mood, we did not count it as a "mismatch" since narrowed range itself is not particularly desirable at face value. Though they were glad the depths of negative mood were no longer there, participants soon began noticing that they also could no longer feel joy, delight, happiness. Thus we were able to document both fairly common experiences such as the inability to cry when the respondent thought it would be appropriate to do so, and uncommon experiences such as those that might contribute to hypomanic or manic reactions on the one hand (marked (m) in Table 1), or mismatches such as complaints about the loss of irritability (at face value a positive effect), on the other. Note that many of the mismatch items (for instance, too much confidence) starred in Table 1 are also

marked as manic symptoms. This again is a matter of degree and context. Manic or hypomanic reactions are extremes of the mismatch phenomenon—mismatching not only the individual's expectations but also societal standards.

Advanced undergraduate students were recruited and trained to code the UPSE portion of the PSEQ on non-data tapes until Cohen's Kappa scores were at least .70 (Streiner & Norman, 1995, pp. 116-122). Coders then rated tapes in four teams of two, with instructions that each team must reach consensus on each item. Teams listened to and coded tapes in their entirety since UPSE information often occurred during open-ended responses outside the section of the interview that dealt specifically with UPSEs. As they listened, each coder took verbatim notes on relevant tape segments, noting the number on the tape counter as they did so, so that they could listen again to problematic passages. The verbatim notes then were the basis for reaching consensus on the points to be coded, with decisions made according to the definitions of items in the coding manual, which specifies that coders take context into account. Twenty-eight tapes that had already been coded by the first author and her assistant were randomly assigned among the teams as criterion checks. Overall criterion reliability was $\kappa = .80$. Coders received undergraduate credit for their work.

Statistical Analyses

SPSS software (version 10.1) was used for all statistical analyses except for Kappas, which were calculated manually. Differences between groups were calculated using a one-way ANOVA with planned contrasts for continuous variables and Chi-square tests for $2 \times n$ contingency tables for categorical variables. Significance levels are all two-tailed.

Results

Most respondents (83%) would have met DSM-IV criteria for major depression (American Psychiatric Association, 1994) prior to being prescribed SSRIs. A noticeable minority (15%) would have met criteria for "minor depression," and about 2% were not depressed at all according to their report of symptoms and the DSM-IV criteria, though their prescriber told them they were. Non-Responders were more likely to be diagnosed with minor depression than were responders (Renewers and Non-renewers combined), $\chi^2 (1, n = 159) = 6.837, p < .01$.

Physical side effects most often reported included sexual dysfunction, dry mouth, jitteriness, nausea, headache, sweating, dizziness, lethargy, and inability to sleep. The unwanted psychological effects most frequently reported by respondents were narrowed range of affect and not feeling like oneself, followed by loss of creativity, increased apathy, and unusually vivid dreams, loss of concentration, ambition, empathy and so forth (see Table 1).

Mismatch items were experienced by 51 (32%) of the sample, and 4 people (2.5%) experienced only mismatch items, in the form of manic reactions to the drug. Of the mismatch items, the most frequently endorsed was the inability to cry (20% of the whole sample), followed by the inability to feel anger or irritation (7%) when it seemed appropriate to do so.

As stated above, participants were divided into two main groups: those for whom the medication worked (addressed their symptoms, n = 92) and those for whom it did not work (n = 69). The two groups were divided further according to whether or not subjects said they would take the same drug again if they were to become depressed in the future.

At face value, one would expect that if the medication worked, people would take it again, and if it did not work, they would not. One subgroup belied this expectation: 43 subjects said they would not take the medication again even though it had addressed their symptoms. We had expected to find this subgroup, however, based on clinical experience. We called this group "Non-Renewers." The other two subgroups were those for whom the drug worked, who would seek re-prescription if they became depressed again ("Renewers") and those for whom the drug did not work, so they would not seek re-prescription if they became depressed again ("Non-Responders"). The subgroups were demographically equivalent.

About 90% of all respondents had experienced at least one SE; and about 75% had experienced at least one UPSE. Planned comparisons showed that the mean number of SEs and UPSEs experienced differed by group (equal variances not assumed, see Table 2). As expected, Renewers experienced significantly fewer SEs than either of the other groups, $t\ (128) = 3.995$, $p < .001$. And as expected, Renewers experienced significantly fewer UPSEs then either of the other groups, $t\ (129) = 4.607$, $p < .001$. Contrary to expectations, however, Non-Renewers and Non-Responders did not differ in the number of SEs experienced. Also contrary to expectations, Non-Responders experienced significantly more UPSEs than either Renewers or Non-Renewers, $t\ (121) = 2.818$, $p < .01$.

To tease out something of the relationship between side effects and satisfaction with the treatment, (as willingness to prescribe again should depression return in the future), we asked participants their primary reasons for stopping the course of medication (see Table 3, Primary Reasons For Quitting). As expected, most (18/33) of those who

quit because the drug "did not work, quit working, or was not working enough," belonged to the Non-Responder group. Most (17/20) of those whose primary Reason for Quitting (RFQ) was "felt better," as expected, belonged to the Renewer group.

However, what interests us in this study is any differential pattern among those participants who claimed SEs or UPSEs as their primary reason for quitting, a total of 88 subjects (Figure 1). It appears that groups and RFQs were significantly related, χ^2 (2, n = 88) = 12.967, p = .002, with Non-Responders (n = 44) quitting more often due to UPSEs than to SEs, Non-Renewers (n = 29) and Renewers (n = 15) quitting more often due to SEs than to UPSEs. Although respondents with minor or subsyndromal depression fell mostly in the Non-Responder group, as mentioned above, the pattern of quitting due to UPSEs held for Non-Responders regardless of symptom level. This pattern did not support the hypothesis that a majority of Non-Renewers might be quitting and refusing to re-prescribe because of UPSEs, though this was the case for 24% of our sample of Non-Renewers.

The length of time that participants stayed with their treatment is also revealing (see Table 4). Twenty-five percent of the total sample (40 subjects) quit in less than 12 weeks: 80% of these (32) were Non-Responders, 20 of whom quit in 4 weeks or less. UPSEs were the most frequent reason that Non-Responders quit before 12 weeks (15 Non-Responders), followed by SEs (10 Non-Responders). Only 5 Non-Responders claimed to have quit in these first 12 weeks simply because the drug was not addressing their symptoms.

Of the 121 (75% of the sample) who lasted at least 12 weeks, 31 (26%) claimed SEs as their primary RFQ, while 28 (23%) claimed UPSEs as primary RFQ. More than

half (57%) of those quitting because of UPSEs after at least 12 weeks, again, were Non-Responders, and about a third, Non-Renewers. Non-Renewers lasting at least 12 weeks quit mostly because of SEs (40%), followed by UPSEs (20%). Of the Renewers lasting at least 12 weeks, about a third quit because they felt better, followed by SEs (22%).

Discussion

This study found unwanted psychological side effects to be just as important as physical side effects to participants in our sample when they reported their reasons for quitting. Thus, in accordance with other studies, we found side effects to be the most common reasons for quitting SSRIs taken for depression (Basco & Rush, 1995; Johnson, 1981). This study presents evidence that psychological side effects might well be included in measures and discussions of side effects in general, even though (except for the manic syndrome) they present no known physical danger to the patient.

Because this study relied on self-report, we cannot determine whether unwanted psychological effects were in fact due to drug action or were a misattribution by patients. Still, it may be irrelevant since these experiences were reported to affect decisions to stop taking the medication in a significant number of respondents in our sample. This is in accord with other studies of subjective responses to medication and their effect on adherence (Hogan & Awad, 1992; Hogan, Awad, & Eastwood, 1983; Van Putten & May, 1978; Van Putten, May, Marder, & Wittman, 1981). Objective measures may show that the effect was in fact not due to the medication, and that refusing to take or return to the medication is objectively unwarranted. Nonetheless, adherence is affected.

In the present study, Non-Renewers and Non-Responders both experienced about the same numbers of SEs and UPSEs. Remarkably, when the medication was not

addressing symptoms of depression (in the case of Non-Responders), and if physical side effects were not too extreme, participants were more likely to attribute their wish to stop medication to unwanted psychological effects than to the fact that depression symptoms were not improving. Many people seemed to be remarkably patient under these circumstances, continuing to take medication that apparently was not addressing their symptoms even longer than 12 weeks before deciding to quit. This casts some doubt on the situation. Do patients not identify depression symptoms as the problem? A possible explanation is that if the SSRI is not changing features of the depressive experience, additional undesired changes in the same domain become more salient. Conversely, if the SSRI is addressing the depression symptoms perhaps aversive changes in adjacent private domains become more salient (dry mouth, lethargy, sexual dysfunction), which might account for physical side effects being cited more often by Non-Renewers as the reason for quitting.

Future research might include a larger, random and more representative sample to determine the prevalence of UPSEs in patients taking SSRIs and other medications, and the possible relationship of UPSEs to adherence to treatment, or, for instance, to suitability of patients for psychosocial interventions. One drawback of the measure as it exists is the categorical nature of the data obtained. Another version with, for instance, Likert-type scaling of the salience or emotional valence of the UPSE might permit more sophisticated statistical analyses. Additionally, a sufficiently large sample might allow a factor analysis of the list of UPSEs that would shed more light on these phenomena.

Table 1. UPSEs in order of frequency reported.

UPSE	%	(n)	UPSE	%	(n)
Narrowed range of affect	46.0%	(74)	Loss of enjoyment	6.2%	(10)
Not feeling like self	32.9%	(53)	Can't express opinions	5.6%	(9)
Loss of creativity	24.2%	(39)	Racing thoughts (m)	5.6%	(9)
*Inability to cry	20.5%	(33)	Loss of confidence	4.3%	(7)
Apathy	18.6%	(30)	Loss of self esteem	3.7%	(6)
Vivid dreams	18.0%	(29)	*Too confident (m)	3.7%	(6)
Loss of concentration	17.4%	(28)	Increased crying	3.1%	(5)
Loss of ambition	16.1%	(26)	*Goal directed activity ↑ (m)	3.1%	(5)
Loss of empathy	14.3%	(23)	Risky enjoyment ↑	2.5%	(4)
Increased anger	13.7%	(23)	*Inflated self-esteem (m)	1.9%	(3)
Memory loss	13.0%	(21)	*Too opinionated (m)	1.9%	(3)
Anxiety	11.8%	(19)	*Euphoria (m)	1.9%	(3)
Dissociation	9.9%	(16)	*Too creative (m)	1.2%	(2)
Can't work on problems	9.9%	(16)	*Hyper-concentration (m)	1.2%	(2)
*Loss of anger, irritability	6.8%	(11)			

* paradoxical "mismatch" items; (m) hypomanic or manic symptoms

Table 2. Mean number of SEs and UPSEs experienced

Groups	Mean (SD) # SEs Experienced	Mean (SD) # UPSEs Experienced
Non-Responders (n = 67)	3.9 (2.8)	4.0 (3.1)*
Renewers (n = 49)	2.5 (1.8)**	1.9 (1.9)**
Non-Renewers (n = 42)	4.0 (2.9)	3.5 (3.1)

**$p < .001$; *$p < .01$

Table 3. Primary Reasons for Quitting SSRI treatment

		didn't work	felt better	SE	UPSE	other	Total
Non-Responders	n =	18	2	13	31	5	69
	% =	26%	3%	19%	45%	7%	100%
Renewers	n =	8	17	12	4	8	49
	% =	16%	35%	25%	8%	16%	100%
Non-Renewers	n =	7	1	18	11	6	43
	% =	16%	2%	42%	26%	14%	100%
Total	n =	33	20	43	46	19	161
	% =	20%	12%	27%	29%	12%	100%

Table 4. Reasons for Quitting before and after 12 weeks of treatment (Percentages are of the total sample.)

Reasons For Quitting	<12 wks	>12 wks	Total
	n (%)	n (%)	n (%)
didn't work, quit working	6 (4%)	27 (17%)	33 (20.5%)
felt better	2 (1%)	18 (11%)	20 (12.4%)
SE	12 (7%)	31 (19%)	44 (27.3%)
UPSE	18 (11%)	28 (17%)	44 (27.3%)
other	2 (1%)	17 (11%)	20 (12.4%)
Total	40 (25%)	121 (75%)	161 (100%)

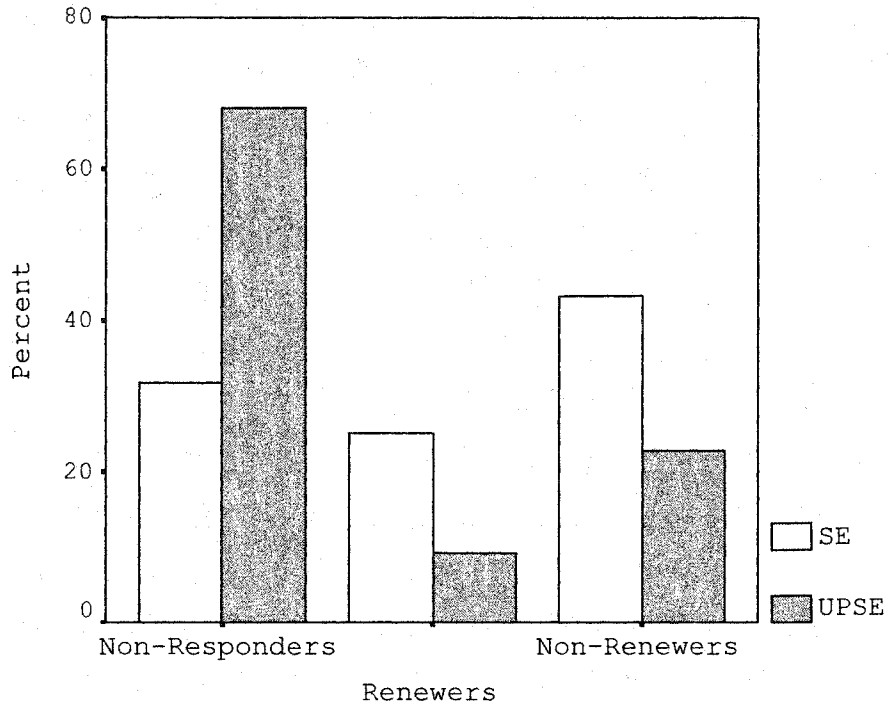

Figure 1: Reasons for Quitting: SEs vs UPSEs by group.
(Non-Responders n = 44; Renewers n = 15; Non-Renewers, n = 29.)

Chapter 2: Development of the PSEQ

To complete the background for the construction of the PSEQ, this section continues with a review of side-effect rating scales and literature on psychological side effects of antidepressants. (Literature on patient discontinuance of antidepressant medications was reviewed in the opening chapter.)

Antidepressant side effects and rating scales

The term "side effect" is derived from the notion of adverse drug reactions, defined as "any noxious, unintended, and undesired effect of a drug, which is observed at doses usually administered in man" [emphasis added] (Lingjaerde, Ahlfors, Bech, Dencker & Elgen, 1987, p. 11; see also Dukes et al., 1996). Lingjaerde and company state from the outset that, "the association between the drug and the symptom or sign in question may be difficult to assess." This is a major issue in the construction of side-effect assessment measures.

At least three prominent pharmacotherapy researchers have reported that their own informal observations are consistent with our hypothesis about the existence of unwanted psychological side effects (UPSEs), namely Alan Gelenberg (private communication), Anthony Rothschild (private communication), and David Dunner (private communication). Finding out more about this issue in a systematic way may affect the way we go about obtaining treatment for depression and it may help improve adherence to treatment.

One other group of researchers is known to be working with similar phenomena (A. Gelenberg and C. Laukes, private communication). However their measure was not

available for our use, nor does it address the contextual or adherence aspects of psychological side effects as our measure was designed to do. Their work, however, does corroborate the existence of the domain of interest to us, namely subtle, unintended psychological effects of SSRIs.

The subtler cognitive phenomena that we call "unwanted psychological side effects" (UPSEs) may overlap with what is referred to as antidepressant tachyphylaxis or break-through depression (Byrne & Rothschild, 1998; cf. Golden, 1998) humorously referred to as "Prozac poop-out" (Rothschild & Byrne, 1999), which may actually be a tolerance or withdrawal effect, or "discontinuation syndrome" (Rosenbaum, Fava, Hoog, Ascroft, & Krebs, 1998). Hence it is necessary to ask about the subject's experience prior to medication to be sure that what they report is not merely an untimely reappearance of symptoms for which they originally sought treatment. Most of the anecdotal reports we have and are interested in documenting do not actually map onto the symptoms used for diagnosing depression, so the overlap with so-called break-through depression may not be relevant. An exception would be when patients report depression symptoms they did not have in their original constellation of symptoms, but that occurred after taking SSRIs.

Observer-rated side-effect scales. The psychological side effects we are interested in documenting are not routinely listed in standardized side effect measures such as DOTES-TWIS (Guy, 1976), and the extensive SAFTEE physician interview (Levine & Schooler, 1986). The Dosage Record and Treatment Emergent Symptom Scale (DOTES) of the National Institute of Mental Health (NIMH) Early Clinical Drug Evaluation Unit/New Clinical Drug Evaluation Unit (ECDEU/NCDEU) is a physician-rated record

of drug dosage and treatment-emergent symptoms to be used with "all (psychopharmacological) research populations." It was published in 1976, prior to the appearance of the SSRIs that interest us. For each symptom that is present at each assessment point, on this measure, the rater notes intensity (mild, moderate, severe) and degree of relationship between the drug and the symptom (on a 5-point scale: none, remote, possible, probable, and defined) with percent probability specified for each point. There is also a code for subsequent action taken. The Treatment Emergent Symptoms Scale (TESS) Write-In (otherwise known as the TESS Write-In Scale or TWIS) is an independently formatted 6-item scale to be used in conjunction with the DOTES whenever it is necessary to record treatment emergent symptoms not printed on the DOTES. The TWIS follows the same format as the DOTES with regard to intensity, degree of relationship between drug and symptom, and action taken. Hence, in order to have recorded the kinds of effects we are interested in, a research physician would have to notice and consider the effect relevant enough to write in. Because the context (side effects printed in the DOTES) is a list of side effects that are potentially dangerous to the subject's physical health, we suspect it would be highly unlikely that the psychological effects we are documenting would have been reported by the patient and written in by the physician even if they had occurred. This measure is used by research physicians with exacting protocols, so the exact dosage taken and recorded is relatively controlled. However there is no provision for possible patient non-adherence (cf. Engstrom, 1991).

The Systematic Assessment for Treatment Emergent Events (SAFTEE) interview was developed by Levine and Schooler (1986) to address some of the shortcomings of the

DOTES in side-effect reporting during clinical trials. At that time no single psychopharmacological side-effects assessment scale had yet achieved widespread acceptance and use, though the DOTES-TWIS was the most widely used in clinical trials to that point. One of the main objections to the DOTES was that there were no specific instructions for the interviewer. Thus, some interviewers might methodically ask about each possible symptom, whereas others might only inquire in a very general way about symptoms salient to the patient—both could fill out the forms adequately. Nor was it known whether specific or general inquiry produces more valid detection of side effects, and strong arguments existed for both methods. Hence, Levine and Schooler constructed two forms of their measure, both employing standardized inquiry procedures: the SAFTEE-GI (General Inquiry) and SAFTEE-SI (Specific Inquiry).

In both forms, the questions to be asked are written on the left side of the page in the exact way they are to be asked of the patient. The General form consists of standardized opening remarks and three standardized general inquiries such as, "Have you had any physical or health problems during the past (specified interval)?" The Specific form uses the same opening and general inquiry questions, followed by specific inquiry into possible symptoms in each of 12 bodily systems, plus an "Other" category (accidental injury, attempted suicide, fever, intercurrent illness, medical or surgical procedure, or other write-in). Questions for eliciting onset, duration, pattern, current status, severity, functional impairment, possible contributory factors, relationship of drug to event, and action taken are all specified along the top edge of the page. Although this scale in its thoroughness may be more likely to elicit reports of subtle psychological side

effects, the fact that it specifies "adverse health events" may still preclude their inclusion. The fact that it is designed to be administered by physicians employed in clinical trials further creates a context for preferential reporting of bodily symptoms only. One virtue of the SAFTEE measure is that all reports of adverse health events elicited are recorded regardless of whether they are suspected to be drug related or not. This would serve to remove another source of rater variance. Because it is so specific and comprehensive, it is quite complex and daunting in appearance, though the authors claim that in practice much may be skipped in order to report what is actually going on with any given patient.

Open-ended narrative reporting forms such as that supplied by the Food and Drug Administration (FDA) medical products reporting program, MedWatch (US Department of Health and Human Services, 2001), though much simpler, are also not likely to tap specifically into the subtle psychological effects dimension. It is designed to be used by user-facilities, distributors and manufacturers for mandatory reporting of adverse events, and/or for voluntary reporting by health professionals of adverse events. Degree of relatedness to the drug or device being reported is not rated in this measure. Each page of the MedWatch form contains this note:

> Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Such a note, plus awareness that the report is intended for the FDA, make it likely that reporters would report only those adverse effects relevant to a governmental body, hence actionable effects that may affect a person's functioning permanently, rather than the

relatively harmless matters that interest us, such as a sense of dissociation or lack of creativity.

In 1980 the Committee on Clinical Investigations (Udvalg for kliniske undersøgelser; UKU), a standing committee under the Scandinavian Society of Psychopharmacology, began developing a comprehensive psychotropic side effect rating scale (Lingjaerde et al., 1987) with well-defined items and scale-steps, to be used both in clinical drug trials and in routine clinical practice. It has been shown to have good psychometric properties. It was developed after the DOTES and was still in development just before the SAFTEE scale was published, and was thus able to address some of the problems occurring in both of these. Interestingly, the authors of the UKU scale acknowledge the existence of placebo side effects in clinical trials and suggest ways to correct for these (at least in crossover studies). This scale does rate an item called Emotional Indifference, "a diminution of the patient's empathy, leading to apathy," which directly addresses the kind of phenomenon we are interested in, although we believe there are more dimensions than indifference and apathy. Further, the phrasing, "diminution of empathy, leading to apathy" does not fit our subjects' descriptions. Rather, they tended to report apathy leading to lack of empathy, in reverse of the UKU description.

The UKU scale is a physician-administered structured interview presenting symptoms, degree of presence (0-4, none, mild, moderate, severe), and a physician rating of causal relationship to medication (improbable, possible, probable). Although it is still probably the most comprehensive side-effects scale so far developed, one drawback is that it can take 30-60 minutes to administer, and is usually done by a trained psychiatrist.

For antidepressant side effects specifically, the three existing scales are by Waldron and Bates (1965), Åsberg, Cronholm, Sjöqvist, and Tuck (1970), and Bech (1984). The Waldron and Bates scale was a checklist of known physical side effects of tricyclics, designed to show if there was a different side effect profile for two tricyclics. The Åsberg scale defines 11 items on a 4-point scale (0 – 3) and is scored by a summed total. However a summed total score does not discriminate different side effect profiles for different drugs. Only the Bech was designed for use with an SSRI (the trial compared citalopram and clomipramine), but it is basically a modified Åsberg scale.

Self-rating scales. There are only two self-rating side-effect scales referred to in the literature. The Texas Medication Algorithm Project (TMAP), an ongoing project to test and evaluate the clinical and economic impacts of algorithm-based treatment, has developed patient and family education materials including a symptom and side effects monitoring sheet for depression (Rush et al., 1998). Patients are asked to list the 3 most bothersome symptoms (of depression) in the last week, and overall how severe these were; and they are to list the 3 most bothersome side effects in the last week, and overall how severe they were. This would potentially allow for reporting psychological side effects, since the side effect reporting is write-in rather than a checklist. However, on the back of the reporting sheet are illustrated cues for reporting both depressive symptoms and side effects. The cues for side effects point to seven bodily domains plus a hint about weight loss (or gain), with no mention of cognitive effects.

The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS; Day, Wood, Dewey, & Bentall, 1995) was derived from the UKU (Lingjaerde et al., 1987)

rating scale, with items re-written for a self-administered format. It taps into some of the subjectivity involved in patient adherence to medication regimes, and lists "Lack of emotions" as an item. In addition to 41 side-effect items, 10 "red herring" items were included, referring to symptoms that are not known neuroleptic side effects (such as chilblains, hair loss). Instructions are, "Please tick off how much you have experienced the following symptoms over the last month." Items are designed for self-rating on a 0 - 4 scale (not at all, very little, a little, quite a lot, very much). The LUNSERS was found to be a valid and reliable assessment of patients' experiences of neuroleptic side effects.

Although it is not a side effect rating scale, the Discontinuation-Emergent Signs and Symptoms scale (DESS; Rosenbaum, Fava, Hoog, Ascroft, & Krebs, 1998) is a self-report checklist that includes four items reported by our pilot subjects that we identify as UPSEs, namely "Feeling unreal or detached," "Confusion or trouble concentrating," "Forgetfulness or problems with memory," and "Problems with speech or speaking clearly." Whether these effects are due to the drug itself or to drug discontinuance is not clear at this point. Of these effects, only "Feeling unreal or detached" and "Confusion or trouble concentrating" were identified as major discontinuation related events in the Rosenbaum study. However, since that study did not report which DESS items were identified by patients at baseline, and since the mean number of DESS items identified at baseline was a little over 3 (the exact mean was not reported, only shown on a chart), it is possible that these items are actually effects of the medications rather than discontinuation-related events. In any case, these 4 overlap items are among those listed as related to SSRI discontinuation in the reports cited by Rosenbaum et al. in providing

background for the DESS. If we are to identify any of these effects as UPSEs rather than discontinuation symptoms, we will need to ascertain when they appeared in the subject's experience, and rely on the subject's recall of regular adherence to the medication. Only fluoxetine, because of its long half-life, is resistant to discontinuation effects in the event of missing a daily dose (Rosenbaum et al., 1998). The other SSRIs may give rise to discontinuation events when a day's dose is missed. If the subject is not aware of having missed, s/he may report a discontinuation effect as a side effect. Such experiences, even when misreported would, however, be attributed to the medication, which is in any case relevant to the subject's attitude toward the drug in question.

It is interesting to note that the DESS is a retrospective self-report checklist. Patients were asked, "During the past 7 days, have you experienced any changes in the following symptoms?" For each of the 43 DESS items, patients were to choose from four responses: new symptom; old symptom, but worse; old symptom, but unchanged; or symptom not present (Rosenbaum et al., 1998, p. 87). Although no psychometrics were reported for this measure, the authors (and their sponsor, Eli Lilly and Company), relied on its face validity and assumed sufficient reliability to report on these effects, providing us with some precedent for the current project. Also interesting is the fact that DESS items overlap considerably with side-effect lists for SSRIs, and that DESS items are referred to as "signs and symptoms."

We believed it was worthwhile to create a more context-sensitive scale for SSRI side effects. By taking into account the context for the appearance and salience of psychological side effects, the PSEQ locates the patient's perception of causality, and its

effect on adherence (discontinuance) decisions. Whether the experiences are in fact due to drug action itself or are a misattribution by patients may be irrelevant since these experiences do appear to bear some relation to adherence. That is, in the absence of knowledge to the contrary, a person who attributes an unacceptably unpleasant experience to a medication will be less likely to want to take that medication (cf. Hogan & Awad, 1992; Hogan, Awad & Eastwood, 1983; Van Putten and May, 1978).

Furthermore, the effectiveness of an antidepressant agent cannot even be measured if patients fail to follow the treatment regimen. Thus patient compliance is necessarily the most important factor of all (Demyttenaere, 1997, 1998; Demyttenaere et al. 1998; Gardner, 1998; Kupfer, 1995a,b; Lin et al., 1995; cf. Olivier-Martin 1986; Thompson, Buesching, Gregor & Oster, 1996).

Literature on psychological side effects

Apart from side-effects measures already mentioned, there are three small places in the literature that are relevant to the phenomena we wish to document with regard to SSRIs. In the late 1970s, Abrams and Taylor published "A rating scale for emotional blunting" (Abrams & Taylor, 1978), in the context of diagnosing schizophrenia. Although this seems far from relevant to psychological side effects of SSRIs, some of the items that reliably discriminated schizophrenia from mania in Abrams and Taylor's study seem to be describing behaviors that our subjects experienced after taking SSRIs. Unfortunately, this scale was not tested with subjects diagnosed with depression. Some of the items seem to describe the behavior of severely depressed individuals (e.g., "seclusive/withdrawn, avoids social contact," "lacks spontaneity") (Abrams & Taylor, p. 227). Items that map

onto our subjects' SSRI-related experiences include "constricted affect (narrow range)," "difficult to excite emotions/ unresponsive," "indifferent to surroundings," "indifference/lack of affection for family, friends," "indifference/unconcern for own present situation," and "indifference/unconcern for own future (lacks plans, ambition, desires, drive)." Berenbaum and colleagues published a later, factor-analytic study of this scale, to further tease out the nature of emotional blunting in a psychiatric inpatient sample (Berenbaum, Abrams, Rosenberg & Taylor, 1987). The factor analysis identified lack of emotional expression and avolition as the central domains documented by Abrams and Taylor's scale. In a less severely disturbed population, we might see this type of behavior referred to as "apathy and indifference."

Secondly, Marin and colleagues (Marin, 1990a,b; Marin, Firinciogullari, & Biedrzycki, 1993, 1994; Marin et al. 1995) worked toward a careful discrimination of "apathy syndrome" from apathy as a symptom, in literature on geriatric dementia and Alzheimer's disease. Though there is some question about the relation of apathy and indifference to depressive symptoms themselves (Levy et al., 1998; Marin, 1990b), emotional indifference and a narrowed range of affect are some of the experiences patients have reported to us in complaining about SSRI treatment.

Lastly, there are a few articles evaluating SSRIs in comparison with the tricyclic antidepressants (TCAs), in which subjective complaints are mentioned. In 1990, Hoehn-Saric, Lipsey and McLeod reported observing apathy, indifference and disinhibition in case studies of two panic-disorder and three depression patients on the SSRI antidepressants, fluvoxamine and fluoxetine. The authors stated that these were "dose-

related" effects that resolved with adjusted dosages of the medications. However in fact, two of the depressed patients discontinued the SSRI, preferring the sedation of TCAs to the effects of the SSRI. This seems to indicate either the depressed patients' doubt about the effect of an adjusted SSRI dosage, or that the effects did not resolve for them under reduced dosage. In 1994, Nelson published a short review of studies comparing SSRIs and TCAs, questioning the prevailing opinion that SSRIs have a lighter side effect burden. He concluded that though the literature does support this notion, the differences are not as overwhelmingly in favor of SSRIs as might be assumed. Further, he pointed out that more patients taking fluoxetine stopped treatment due to "uncooperativeness" than did nortriptyline patients, and that more studies need to be done on side effects and patient satisfaction, a challenge taken up in a small way in the present study.

Development of the PSEQ

As described in Chapter 1, we developed and pilot tested an instrument to document unwanted psychological side effects (UPSEs) of depression treatment with SSRIs. In addition we assessed the relationship of UPSEs to consumer satisfaction as expressed in willingness to return to the same medication in the event of future episodes of depression. This section fills in a few details about the development of the PSEQ, including the UPSE coding system and manual.

In the course of an earlier depression treatment study (Kohlenberg, 1997-2000), we conducted diagnostic assessments of individuals who self-reported depression. Participants were recruited through referrals from local therapists and clinics, and advertisements in local newspapers and posted flyers. All participants underwent an

initial telephone screening interview with a trained assessor to rule out those who clearly would not meet diagnostic criteria for Major Depressive Disorder, or whose problems included confounding medical diagnoses, or more urgent psychological problems such as current PTSD, psychosis or substance abuse or dependence. Those successfully screened were scheduled for a full semi-structured diagnostic assessment, which was videotaped after written consent was obtained at the beginning of the interview. As part of this larger assessment, we asked the following open-ended questions relevant to the current proposal:

- Was the fact that this is a non-drug study one of the reasons you wanted to participate?
- Why didn't you want to take drugs for your depression?
- If an antidepressant worked before, why didn't you ask your doctor to go back on it?
- If there were no side effects or if you knew you had a chemical deficiency like insulin for diabetes, or a trace mineral for bone growth (something that doesn't reflect on you personally), would you take a drug that corrects that deficiency?

As a first step in developing the PSEQ, the author transcribed the segments of the assessment interview that contained these relevant questions. These 40 transcriptions were subjected to a content analysis (Carney, 1972; Weber, 1990; Wimmer & Dominick, 1997) in order to determine domains of psychological side effects that have affected individuals' decisions to seek non-drug treatment. Content analysis is a method of analyzing written or spoken communications in order to extract themes or conceptual entities that are coherent wholes, but are more easily illustrated than defined. This is most useful when new phenomena are noticed but people are unsure of how to perceive them,

as in our study (Carney, 1972). The process is used systematically to classify the textual themes in question into mutually exclusive, exhaustive categories. Researchers then develop a system of category definitions, and the eventual result is a coherent way of perceiving and counting the phenomenon in question. From there, surveys and other measures may be created in order to track the phenomenon quantitatively.

In the initial content analysis of screening-interview transcripts mentioned above, the author and a non-matriculated graduate assistant (A.R.) concentrated on documenting, describing and classifying those psychological side effects that are not considered medically significant at present, but that affected subjects' decisions about treatment. From these and from reports in the literature and other side-effect scales (Day et al., 1995; Guy, 1972; Hoehn-Saric et al., 1990; Lingjaerde et al., 1987), we extracted 14 preliminary categories of psychological side effects of SSRIs. To these, we added an "other" category in order to elicit reports not yet determined.

The first working iteration. We developed a preliminary version of the PSEQ (see Appendix A) to assess the categories of psychological side effects determined from the content analysis. The questionnaire is similar to existing structured clinical surveys of physical side effects and depressive symptoms (Day et al., 1995; Levine & Schooler, 1986; Lingjaerde et al., 1987; Guy, 1972), and includes a section for reporting known physical side effects of SSRIs (Borg & Brodin, 1996).

The first section covers demographic information and identifies the medication experienced, the status of the prescriber (general practitioner, psychiatrist, nurse practitioner, neurologist, etc.). Next it asks whether the medication worked for the

respondent and whether s/he would take it again in the event of another episode of depression. Further, callers are asked whether they stopped on their own or in consultation with their prescriber. This section also includes inquiry into the frequency and amount of tobacco, caffeine, alcohol, over-the-counter painkiller and recreational drug use. This was to assess possible connections between use of common mood-altering substances and subject attitude toward antidepressant effects.

The second section consists of a list of the 14 derived categories of psychological side effect plus one "other" category. The subjects are asked whether they had experienced the effect prior to taking the medication; whether they perceived the medication effect (if so experienced) as appropriate to the context in which it was experienced; whether they liked the effect or not; and the degree to which each particular effect influenced their decision to stop (or continue) taking the medication and their decision whether or not to prescribe again to the same medication in the future. This section includes considerable write-in space, as early tests indicated that subjects' experiences may be articulated in ways that do not fit the expected categories.

The third section follows DSM-IV (American Psychiatric Association, 1994) criteria for each symptom of Major Depressive Disorder (MDD), asking whether subjects had this symptom prior to taking the medication, or whether it appeared after taking the medication. If they had the symptom prior to taking the medication, they are asked whether the medication changed the symptom, with options ranging from "1 = much worse," through "3 = no change" to "5 = much better." In this way we hope to determine probable diagnostic status when the medication was prescribed, without having direct

access to patients' medical records. We accepted reports from subjects even though they may not fully have met criteria for MDD.

The fourth section of the PSEQ lists physical side effects including an "other" item, and again asks the degree to which the experience of each side effect contributed to the decision to stop taking the medication or not to re-prescribe in future. Following this is a series of questions about instructions given at the time of prescription, patient education about side effects and how to handle them, what to expect about the length of time until effects take hold, length of time the subject should expect to take the drug, instructions about how to take the drug and how often to check in with the prescriber, all in accordance with the study by Lin et al. (1995) that found patient compliance in the first 4 weeks increased solely as a function of patient education on these specific items at the time of prescription.

Finally, the PSEQ asks for a maximum of three reasons for quitting the medication. This is an open inquiry and may include "felt better," "it wasn't working," specific side effects, "it was time to try coping on my own," " insurance ran out," etc.

We are particularly interested that the psychological side effect items present contexts for subject's responses. Where some measures ask, for example, whether a person is able to cry "not at all," "less than usual," "about the same as usual," or "more than usual," they neglect to inquire about the perceived appropriateness of the situation. For example, a person may report that they are able to cry "about the same as usual," but in their opinion they have been crying inappropriately for years. Or perhaps they have been able to cry "much more than usual"—but the occasion warranted it. Our survey

attempts to document the subject's perception of appropriateness as context for responses and whether they liked the effect or not. This should add to our knowledge of patient satisfaction with SSRI treatment for depression.

To review, the current iteration of the PSEQ consists of: 1) demographics, type and timing of SSRI experience (must be reporting on a past experience so as to report reasons for ending treatment); 2) semi-structured interview about unwanted psychological side effects (UPSEs), with options for reporting items not listed, including assessment of how much the effects experienced (if any) contributed to decisions to stop or not re-prescribe to the medication in question, the perceived situational appropriateness of the symptom or drug effect in question, and whether the subject liked the effect or not; 3) assessment of symptom state prior to starting the medication, and degree to which the drug changed each item in the symptom list (with option to report that a symptom was only experienced after starting the medication); 4) physical side-effect checklist (including "other" category for open reporting); 5) questions about education and instructions received about the medication regime; and 6) assessment of how much the effects experienced (if any) contributed to the decision to stop or not re-prescribe in future to the medication in question, through inquiry into a maximum of three main reasons for quitting the medication, plus an open-ended miscellaneous question to elicit additional information.

The PSEQ was originally designed to be a pencil-and-paper self-report measure. However in a small pilot run of three volunteer subjects, it became apparent that the questionnaire was far too complex for any but dedicated researchers to fill out accurately.

Because the author had considerable experience in telephone interviewing of depressed subjects and in eliciting subject response via semi-structured interviews such as the SCID-I and II (Spitzer, Williams, Gibbon, & First, 1992), we decided to administer this iteration of the PSEQ as a semi-structured telephone interview instead. After some practice, all the relevant information could be elicited in an average of 40 minutes. We obtained Human Subjects Review Board approval to record the interviews after obtaining explicit consent to do so, so that the recordings might be used as data, and then further reviewed and content-analyzed to produce another iteration of the PSEQ in future—possibly one more amenable to a paper-and-pencil self-report format. However at this stage our unique interest in the context of responses made oral interview by an experienced and knowledgeable interviewer mandatory.

Participants. We intended to recruit 50 patients in four specific patient samples (see Figure 2) for an extreme-groups validation.

The first group were Dropouts/Nonresponders: those who were diagnosed with Major Depression and prescribed SSRIs, but who dropped out of treatment before symptom reduction could be detected (label A in Figure 2), whether the trial time was adequate or not.

The second group were Non-Adherent Responders: those who were diagnosed with Major Depression and prescribed SSRIs, who achieved acute symptom reduction and discontinued treatment without medical consultation (even though continuance was recommended or expected), and who would re-prescribe in future to treat depression. (label B in Figure 2).

The third group were Compliant Responders: those who were diagnosed with Major Depression and prescribed SSRIs, who achieved acute symptom reduction, discontinued treatment with medical consultation and who would re-prescribe in future to treat depression. (label C in Figure 2).

The fourth group were Non-Renewing Responders: those who were diagnosed with Major Depression and prescribed SSRIs, who achieved acute symptom reduction, discontinued with or without medical consultation but would not take SSRIs again in the future should relapse occur (label D in Figure 2).

We placed advertisements as described in Chapter 1, and within the first week of interviewing it became apparent that the four a priori groups were not going to be available outside of a research context. Few prescribers stipulated the length of a course of treatment; those who did varied in the recommended length from "6 weeks" to "the rest of your life," and many left the decision to quit up to the patient. Hence the concept of quitting against medical advice (the original grouping variable) was not a valid one. Nonetheless, the process of recruiting had begun, and neither funding nor time would allow us to stop subject flow in order to re-think the design. Thus we continued to interview all qualified callers and decided to pursue at least a descriptive study, hoping that some form of group comparison would still be possible. The actual groups obtained for analysis, as described in Chapter 1, are shown in Figure 3.

Preparation of the UPSE coding sheet and manual. As mentioned in Chapter 1, the 29 items for the Unwanted Psychological Effects (UPSE) part of the PSEQ were generated through an iterative process of content analysis. After the first two weeks

(interviewing continued over the next 9 months) of telephone interviews had been conducted, the author and a second non-matriculated graduate assistant (R.F.) listened to the tapes independently, taking extensive notes on UPSEs. Each then made a tentative list of categories so that all UPSE experiences could be coded, until we obtained a mutually exclusive and exhaustive set of categories. These were refined in a series of meetings over the next two months, during which time we produced several versions of the coding sheet. Each time, we coded one or two data tapes and sought resolution to problems in coding until we had a reasonably stable set of categories.

The present version of the coding sheet was deemed adequate for the next stage in the process. The author and R. F. then produced the coding manual (both coding sheet and manual are attached in Appendix B) to define the 29 categories in this version. At this point, we recruited and trained undergraduate research assistants and pursued data collection on the UPSE portion of the PSEQ as reported in Chapter 1.

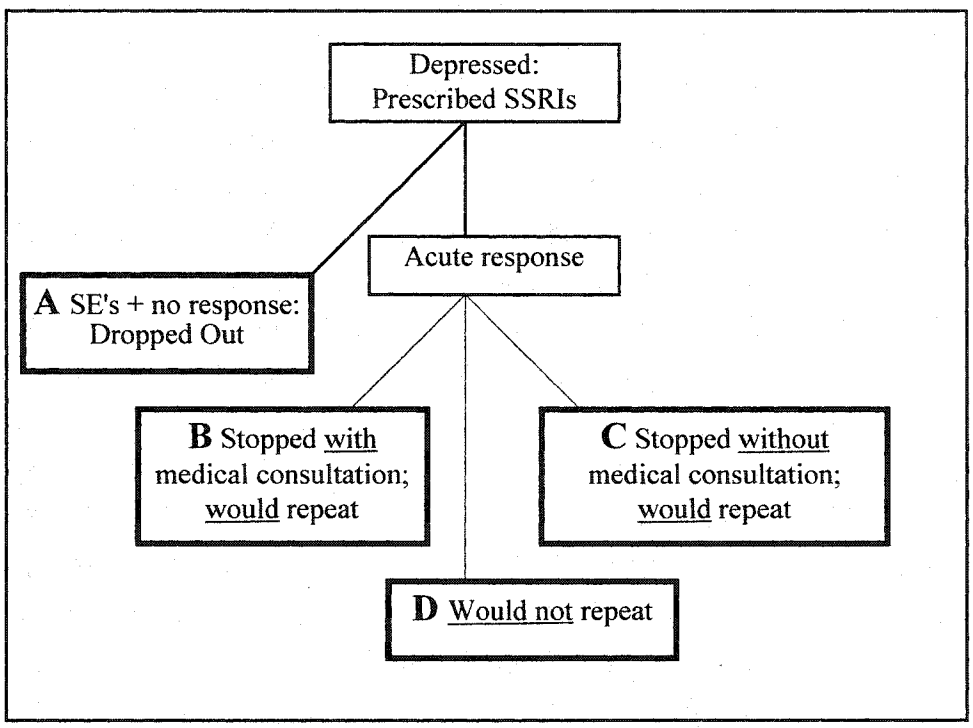

Figure 2. Groups hypothesized a priori for original design.

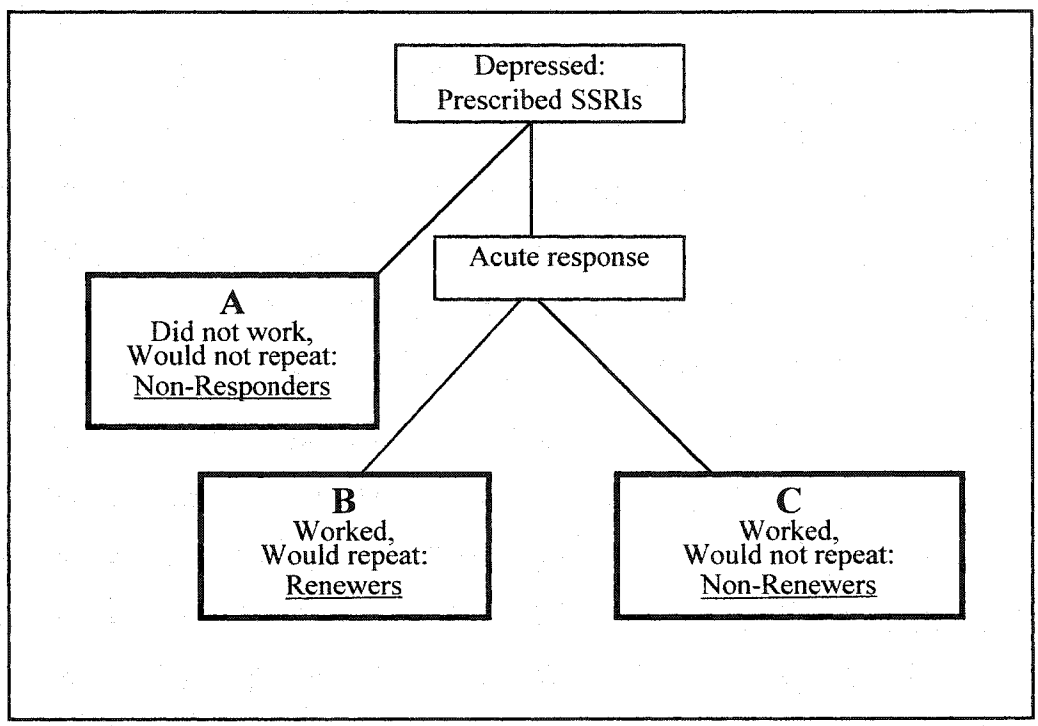

Figure 3. Groups obtained for analysis

Chapter 3: The Construct of Depression: Implications of the PSEQ

Major depressive disorder will be experienced by 17% of the population sometime in their lives, 10% of the population within any given 12-month period (Johnson, Weissman, & Klerman, 1991). These figures do not include sub-syndromal depression and mixed anxiety depression, though these too are widespread, significant illnesses (American Psychiatric Association, 1994; Angst, Meri Kangas, & Preisig, 1997) that are typically treated in the same pharmacological manner as major depression. The profound functional disability experienced by patients often increases the morbidity associated with other diseases (Johnson, Weissman, & Klerman, 1991; Broadhead, Blazer, George, et al., 1990; Sullivan, et al., 1999) and decreases patient motivation for and compliance with medical treatment (Gardner, 1998). While treatment is expensive, whether by medications or by psychotherapy, untreated depression is more expensive, both in direct and indirect costs (Gardner, 1998; Johnson, Weissman, & Klerman, 1991). Given the prevalence and costs of depression, effective treatment for it is among the most important needs in mental health.

Most depression in the US is treated with antidepressant medication. Although medication apparently works adequately for some, (American Psychiatric Association, 1993; Frank, Karp, & Rush, 1993), many patients are not satisfied with it. In 1999 the National Depressive and Manic-Depressive Association conducted an online survey of nearly 1,400 patients who were taking an antidepressant or had received antidepressant treatment within the previous 5 years. Forty percent reported no improvement in fatigue and loss of energy, and 81 percent reported that their depression continued to impair their social life "moderately" or "extremely" while taking antidepressants; 79% reported that

depression still affected their family life, and 72% reported that depression still impaired work performance when they were on antidepressants (Reuters Health, 1999). This was a report on all types of anti-depressant, however our interest is in the selective serotonin reuptake inhibitors (SSRIs).

Although we speak of "depression" as though it were a known object, this is not precisely the case. "Depression" in the clinical context is a construct based on the practice of using the Diagnostic and Statistical Manual of the American Psychiatric Association (APA), now in its fourth edition (APA, 1994). This practice has many benefits, especially in increasing the reliability of diagnosis immensely regardless of the clinician's theoretical orientation, thus improving scientific communication and making mental/emotional disorders amenable to controlled scientific study. However as critics have noted, reliable diagnosis does not adequately deal with some questions of validity (Brown, 1990), since it tells us nothing of etiology and therefore nothing about appropriate treatment. Our survey of consumer experience of and satisfaction with SSRI treatment opens certain questions about the ecological validity of the construct of depression as mental illness and its treatment implications.

In the DSM-IV (APA, 1994), depression (Major Depressive Disorder, adult) is defined as follows:

> Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:
>
> (1) depressed mood most of the day, nearly every day;

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day;

(3) a change of more than 5% of body weight in a month when not dieting, or decrease or increase in appetite nearly every day;

(4) insomnia or hypersomnia nearly every day;

(5) psychomotor agitation or retardation nearly every day (observable by others);

(6) fatigue or loss of energy nearly every day;

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick);

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day;

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide (p. 327).

Problems with this Model

The practice of diagnosing by symptom list carries with it the dangers of reifying a construct and basing arguments on circular reasoning. For example, if a person has experienced the required five symptoms for at least two weeks in a row, s/he receives a diagnosis of "Major Depression." If s/he then asks, "why can't I concentrate on anything these days?" s/he may be told, "because you have Major Depression." Such answers, comforting though they may be to some, do not tell us the causes (functions) of behavior.

Unless we can discern the causes or functions of problematic behavior, we cannot work with the effects with any kind of confidence in the results. Under the DSM system, however, the implications seem to be that if the patient no longer meets diagnostic criteria, the problem is treated. Although this may be valid for some physical ailments, it is not necessarily so for mental/ emotional problems, which call for a broader conceptualization. Guidelines on the treatment of depression from the Public Health Service (Depression Guideline Panel, 1993) state:

> The key initial objectives of treatment, in order of priority, are (1) to reduce and ultimately to remove all signs and symptoms of the depressive syndrome, (2) to restore occupational and psychosocial function to that of the asymptomatic state, and (3) to reduce the likelihood of relapse and recurrence (p.1).

In our observations of people treated with SSRIs, objective (2) does not always follow satisfactorily from objective (1). From the outside, and from an actuarial perspective, objective (2) has been reached if the person is once more working and relating to others. However, although some patients may be functioning better at work and at home following medication, and symptoms may be noticeably reduced, they and their close associates may not perceive this state as the same as their normal, asymptomatic functioning, and are troubled by it. In response to our study questions, for example, these individuals complained of changes in behaviors such as increased ego-dystonic gregariousness and decreased (or increased) time spent in goal-directed activities, loss of tendency to spend time in creative endeavors, loss of caring about others, and the like.

The DSM-IV was not intended to offer or imply treatment recommendations or to specify the mechanisms causing the appearance of the disorder syndromes, having been

conceived as a tool for all clinicians regardless of theoretical orientation (American Psychiatric Association, 1994, pp. xvii-xviii). The implication of a diagnostic symptom list, however, is that the entirety of the problem lies in the symptoms themselves. Thus, antidepressants are prescribed because they may ameliorate the symptoms that constitute the DSM diagnosis of depression, and when symptoms lessen or disappear, the treatment is considered successful. Clinical trials and treatment comparisons are based on this assumption. On the other hand, critics have long argued that merely addressing the end effects of psychological difficulties described by the syndromal symptom list is less useful than attending to the causes and maintaining factors of problematic behavior in the individual's life (Hayes & Follette, 1992; Hayes, Wilson, Gifford, Follette, & Strohsahl, 1996; Kleinman & Good, 1985; McKnight, Nelson, Hayes, & Jarrett, 1984). Thus, from this perspective, medication treatment may be seen as a failure (or in any case, not relevant to the consumer) if a patient does not seek re-prescription when experiencing the same set of symptoms in another episode, whereas the treatment had been a success with respect to those symptoms in the earlier episode. Many prescribers recognize that in general, medication is not an ultimate solution to a depressed patient's problems but a means to help patients reach a level of functioning from which they may begin actively working on their problems (American Psychiatric Association, 1993). However the current trend is increasingly toward strictly biological treatment guidelines, such that medications are expected to create not only biological but also psychosocial improvements in depressed patients (see Rush et al., 1998; cf. Persons, Thase & Crits-Christoph, 1996). We have anecdotal evidence, detailed later in this chapter, that

psychosocial improvements that come about as a result of medication may themselves be problematic.

In addition to telling us nothing about the context for the appearance of symptoms, the DSM diagnosis is profoundly culture-bound (Kleinman & Good, 1985). That is to say, this definition of "depression" is itself set in a context of Northern-European American (referred to hereafter as "Euro-American" or "mainstream") medico-scientific culture and our cultural expectations of illness behaviors (cf. Kleinman, 1985; Landrine, 1992/1995). That mental/emotional manifestations differ from culture to culture has been amply documented by medical anthropologists and in some of the curious results of cross-cultural epidemiological studies (Cinnirella & Loewenthal, 1999; Draguns, 1994; Kleinman, 1985, 1988/1995; Kleinman & Good, 1985). This is well recognized by leaders in psychiatry and psychology, and in the last 10 years or so this point has been mentioned in theoretical articles. Even in the Introduction to the DSM-IV (APA, 1994, pp. xxiv-xxv) the authors acknowledge that manifestations of mental/emotional problems differ from culture to culture.

But if the symptom-list published in the DSM-IV does not apply to a significant percentage of people in the US and Canada (let alone elsewhere in the world), how can we reliably report diagnoses for people of non-Euro-American cultures? How can we conceptualize treatment? The DSM-IV recommends "clinical judgment." Yet detailed instructions for diagnosis exist for mainstream Euro-American culture, seemingly in an effort to bypass or overcome the inexactitude and unreliability of clinical judgment (cf. Arkes, 1981). The same is not true for patients among us from non-mainstream cultures. This situation also implies that there are underlying entities of disturbance that are not

mapped by diagnostic symptom lists. Although we agree that there is more to a depressed state than a symptom list, the notion of an "underlying disease entity" sounds suspiciously like reification. The primary virtue of the DSM system, reliable diagnosis and scientific communication, is undermined by the necessary acknowledgment of cultural diversity in the manifestation of problems.

Those who doubt the importance of multicultural views may argue that the DSM diagnosis of depression has been reached reliably by a variety of practitioners in a variety of settings, including cultures outside of the North American mainstream (though language becomes an immediate confound, cf. Manson, Shore, & Bloom, 1985). What this amounts to, however, is using a sieve with a particular mesh to catch a specific set of people whose behaviors happen to match the symptom list. Outside of US mainstream culture, definitions and meanings of behavior, illness, the cosmos and the relationship of human with non-human differ. Expectations (of the sufferer, his/her society, and the healer) also differ, and more people slip through the mesh ("fail to meet diagnostic criteria"), leading to "under-diagnosis" or even "misdiagnosis" of problems (cf. Ridley, 1989) when these problems are seen exclusively through the lens of US mainstream culture, that is, the DSM-IV with all of its assumptions.

On the other hand, as a clinician and researcher inspired by the writings of B. F. Skinner, the author and her mentors hold that causes of mental/emotional problems lie in the relationship of the individual and the environment (including not only the natural and social surrounds but also the genetic endowment of the individual and her/his history of experiences). This view is consistent with the functional or contextual worldview described by Pepper (1942), and forms the basis of the behaviorist and developmental

approaches to clinical problems (Ferster, 1972a, 1972b, 1973; Hayes & Wilson, 1994; Hayes, Wilson, & Strohsahl, 1999; Kohlenberg & Tsai, 1991; Kohlenberg, Tsai, & Dougher, 1993; Martell, Addis, & Jacobson, 2001; Moss & Boren, 1972; Skinner, 1953, 1974; Sroufe, 1997). Our belief is that people with depressive syndrome will be helped most effectively by changing their relationship with the environment in the way it needs to be changed (which will vary with the individual, his/her circumstances and history). Changing the body chemistry of a sufferer with medication is only one way of changing relationship with the environment. It appears to work well for many people, and may be the most appropriate treatment for them. But medication treatment is not satisfactory for many others. There is more than one way to accomplish change, and strictly chemical change is unlikely to be functionally relevant for all people who manifest the "depressive syndrome." Evidence suggests that as many as half of the depressed patients who seek treatment do not respond to medication (Fava, 2002, p.128). Nor for all its prevalence has the serotonin deficit mechanism been shown to be an accurate or sufficient account of the cause of depression (van Praag, 1993; cf. Nesse, 1999, 2000). Similarly, serotonin reuptake inhibitors have not been shown to have the selective effects they are advertised as having (Azmitia & Whitaker-Azmitia, 1991; Ichikawa & Meltzer, 1995; Jacobs, 1991).

Behavior analysts, medical anthropologists, sociologists, behavioral ecologists and others have long questioned the constructs and practices of the psychiatric establishment, especially regarding diagnostics and treatment implications thereof (Brown, 1990; Follette, 1996; Follette & Hayes, 1992; Follette, & Houts, 1996; Follette, Houts, & Hayes, 1992; Gergen, 1990; Hayes & Follette, 1992; Houts & Follette, 1998;

Kanfer & Saslow, 1965; Krasner, 1992; McGuire, Marks, Nesse, & Troisi, 1992; McLean & Craig, 1975; McLean, Ogsten, & Grauer, 1973; Mirowsky, 1990; Moss & Boren, 1971, 1972; Nesse, 2000). In actuality, we work with the prevailing system in various states of compromise. Within such work are events that bring the questions raised by the functional view to particular salience. This project arose from just such an occurrence: some participants in a depression treatment study reported unwillingness to seek SSRI treatment again even though it had worked for them during an earlier episode of depression.

Questions Raised by the Reasons For Quitting

Why might 45% of the Non-Responders in our sample have quit for psychological reasons other than the fact that their symptoms weren't improving? (See Table 3) One possible factor is that Non-Responders, who quit more often due to UPSEs than any other group, were more likely to have reported minor or sub-syndromal depression symptoms prior to receiving their prescription than were Responders (27% vs. 11%), and there is little evidence that minor or sub-syndromal depression responds to SSRI antidepressants (Fava 2002). Our data seem to support this notion. Still, it is curious that these participants did not report that they quit because the drug was failing to address their symptoms. Perhaps sub-syndromal depression symptoms are not the most salient features of their experience of discomfort. In addition, Non-Responders who met full criteria for Major Depression also quit more often due to UPSEs than due to SEs. Thus Non-Responders (those for whom the medication was not addressing symptoms) tended to quit primarily because of UPSEs regardless of how extensive their symptoms were. Furthermore, 26% of Non-Renewers quit because of UPSEs, so in spite of the fact that

medication was addressing their depression symptoms, these participants also did not like the psychological effects of the medication. In any case, the treatment was not doing what these participants needed it to do.

What would constitute "getting better" for these people? How do we assess what "getting worse" means if it is spoken of in terms of UPSEs and does not map onto the DSM symptom picture of depression or any other disorder? Is "depression" as described in the DSM what is actually wrong with them, or is this symptom list rather a set of epiphenomena? Could it be that treatment by medication is not relevant to what's really wrong with the suffering person in these cases?

This discussion needs to be tempered with a reminder that 30% of our sample were happy with the treatment, considered that it worked for them and would do it again if they were depressed in the future. An additional 27% of the sample, Non-Renewers, considered that the medication had worked for them this time (more or less), but they would not seek the same treatment again in the future, largely because of side effects, both physical and psychological. The remainder of this chapter considers the implications of some of the UPSEs that were reported, in particular those that support and are explained by the notion of adaptive functions of depressive behavior, both in the individual context and in a genetic survival or evolutionary context.

Interpretations and Implications of Some UPSEs

Some of the unintended psychological effects we documented in this study included reports from nearly a third of the participants that they "did not feel like themselves." Although it is not clear exactly what people meant by this phrase, it might usefully be seen as loss of repertoires.

Irritability. For instance, at least two people complained that their accustomed irritability was reduced or eliminated following medication (an instance of "mismatch"). Friends, co-workers and family members were delighted with the new, mellow personality. This sounds like a positive effect, since most of us would rather be around people with a pleasant interactive style. However these individuals were distinctly uncomfortable with the improved state. They stated that their accustomed ways of interacting with others had been sarcastic and irritated for most of their life and claimed that after taking the drug they did not respond to others with their usual "bite." They missed the old pattern, did not "feel like themselves." We might say that under the influence of medication, the environment no longer elicited important behavioral repertoires in these participants. The positive social attention they received as a result of reduced irritability was not reinforcing for them, and in fact, produced noticeable discomfort. By being chemically blocked from producing irritable responses, these participants experienced loss of repertoires of behavior and apparently did not have alternate repertoires for responding to positive social contact.

On a smaller scale, several people felt that they had lost the ability to be irritable when it would have been appropriate to help them respond in a functional way to various situations. However, unlike the two mentioned above, these participants did not feel alienated from themselves because of the effect. On the other hand, most participants reported loss of irritability as a desirable effect of these medications. These individuals had a history of being reinforced by positive social attention and possibly had not chanced to encounter situations wherein irritability would have been appropriate. The

identical pharmacological effect, then, may be either desirable or undesirable depending on the history of the individual and their current circumstances.

One of the hypotheses offered by evolutionary psychiatry is that depressive behaviors have served to maintain primate hierarchies that forge the group coherence which in turn has promoted the survival of genetic lines. There is biochemical evidence that interpersonal relationships correlate with neurotransmitter balances to support this hypothesis (Gilbert & McGuire, 1998). Specifically, the more that subordinate vervet monkeys showed withdrawal (variously identified as shame or depressive behavior), the more relaxed and non-combative the dominant members of the troop became, which correlated with higher serotonin levels in dominant individuals. When subordinates were not so submissive, dominant individuals displayed irritable behavior (McGuire, Raleigh & Johnson, 1983).

If this were also the case with humans, then removing irritability by artificially increasing serotonin levels would de-stabilize an innate behavioral mechanism of social hierarchy regulation. Removing or blocking such irritability would amount to dislodging an individual from his/her place in the social order. This hypothesis too, would help account for some of the UPSE accounts we recorded. Of course, the possibilities for interpretation are myriad. For instance, suppose that the habitually irritable individual were indeed responding as a dominant organism to perceptions of threat to his position from subordinates. If this perceived threat is a constant in his life, is this a therapeutic issue? Does this individual need to be in a clear leadership position rather than as the middle-of-the-troop office position he is in now? Does he have the capacity to be in a lead position at all? Further, is he feeling distress while on medication because the drug

does not remove perception of threat while it blocks his habitual response to threat? This contributes a possible evolutionary context to the plain behavioral notion of distress due to loss of repertoire. A creative clinician might be able to make therapeutic use of these notions, speculative as they are, if the context of the case warranted such interpretation. Considerable research would still be needed to demonstrate the validity of such a model.

Aesthetics and creativity. Some participants were distressed because of loss of ability to appreciate aesthetic qualities in the environment, for example the particular color of young foliage or the crackle and scent of autumn leaves. One person lost a long-standing ability to appreciate and enjoy jazz. This may be related to the SSRI effect of "taking the edge off" of suffering. "Suffering" includes not only a cognitive component (negative thinking and expectation) but also an emotional one. Emotions may be thought of as particular qualities of auto-receptive sensory experience (Skinner, 1953, p. 160f). Fine attention to qualities of sensory experience is required for aesthetic appreciation. To the extent that these antidepressant drugs reduce the emotional aspects of the experience of suffering, they may be thought of as reducing the sensitivity to qualities of sensory experience. That these reductions are not limited to the aversive end of the emotional spectrum is borne out by other evidence: Nearly half of our sample (46%) complained of a narrowed range of affect (see Table 1), such that discernment of joy and delight as well as of suffering, was reduced or no longer functioning.

It seems that across sensory modalities, the kinds of discernment that contribute to aesthetic endeavors (whether appreciative only or appreciative and productive) were often dulled for those in our sample. Almost a quarter of the participants—writers, musicians, painters, and dancers—complained of loss of creativity while taking SSRIs,

threatening their livelihood and sense of well being. Aesthetic experience is an important reinforcer for many people. If a drug blunts the extremes of emotional experience or sensitivity to all kinds of sensory experience, it is likely to result in loss of important repertoires for such individuals. In such cases, SSRI treatment may not be indicated, since loss of sources of reinforcement from these accustomed and highly developed repertoires, in turn, may contribute further to depressive behaviors (Ferster, 1974).

Motivation. Skinner (1953) views creativity as a pattern of having been reinforced for producing new (heretofore unreinforced) responses in a particular realm, such as music, graphic art, dance, writing, acting, etc. This might be thought of in common terms as willingness to following new impulses based on sensory discernments in the realm of the particular art. Not only might the above-mentioned reduction of sensory discernment interfere with such a process, but a general loss of ability/willingness to follow or undertake new behaviors would also shut down creative behavior. Such lack of motivation was reported not only by others besides creative people in our sample, but also by patients elsewhere in reports of SSRI side effects (Gelenberg, 1991; Hoehn-Saric, Lipsey & McLeod, 1990). Marin and colleagues (1990a,b; 1993; 1994; 1995) undertook extensive study of apathy as a psychiatric symptom and a proposed syndrome in the context of various dementias. Although elsewhere the term "apathy" is used to mean "loss of interest" or "loss of emotion," Marin determined that the functional effect of either of these is loss of motivation (1990a).

The list of UPSEs we derived included *apathy* (which we defined as "not caring"), experienced by 19% of the sample; *loss of ambition* (16%), and *loss of confidence* (4.3%). All of these share a component, and in some future factor analysis

may fall into a cluster, of "loss of motivation." Since "motivation" is understood by behaviorists as the availability of reinforcement under a condition of deprivation (Skinner, 1953; 1974), it may be that in the case of lost creativity, loss of repertoire is experienced due to loss of reinforcer potency or availability. That is, if the interrelationships of subtle qualities of sensory experience become unavailable through chemical blunting, the discriminatory stimuli for new (creative) behavior also are not available. Even though complex, shifting interrelationships of sensory experience still occur in the environment around a creative person, they will have lost their potency as reinforcers if those subtleties cease to be perceptible. This may have been at least part of what our participants were reporting as "loss of creativity," and it may be responsible for a percentage of the "apathy" many reported as aversive.

Empathy. A number of people (14%) complained of loss of empathy, or the ability to understand the emotional state of another (cf. Skinner, 1953, p.301) something particularly important in their various human service occupations including parenting, social work, nursing, and teaching. Subtle social cues to the emotional state of the other are readily discriminated by some people, a skill that is reinforced in certain occupations, eliciting therapeutic or nurturing behaviors in response. If one of the effects of the SSRI is to reduce sensitivity to qualities of sensory experience, it may have the effect of reducing those interpersonal discernments necessary to empathy. This is a double-edged blade. On the one hand, a person may no longer feel interpersonal slights as cuttingly as s/he did prior to taking the antidepressant—in many cases, a desirable effect for a depressed person. And on the other, such subtle discernments may be part of a repertoire central to her/his livelihood.

Some participants claimed that though they were in therapy while on the medication, they felt in retrospect that it had been wasted, as they had made no progress during that time. This may have been due to an inability to contact painful feelings—generally considered a positive effect of antidepressants. This would be another instance of what we called "mismatch," the paradoxical dislike of intended drug effects. Once again, the mechanism may be the dulling of sensitivity to sensory experience.

Sociability. Some women reported having become more outgoing and socially oriented, to the delight of friends and co-workers. Unlike those who complained of the loss of accustomed irritability, these participants only complained in retrospect: After stopping the course of medication, the participants were "appalled" at their recalled behavior, though they apparently enjoyed themselves at the time. Usually people who experienced a manic or hypomanic reaction report dismay only in retrospect, however friends and colleagues are concerned, not delighted, when they observe the unusual behaviors. The reported new sociability of these few women had not alarmed their friends and co-workers, so probably it was not outside the normal range. Yet for these participants in their normal, non-medicated, non-depressed state, it had been "too much."

The hypothesized hierarchy-maintenance functions of depression may help us understand the reactions of these participants. To the extent that women are still raised and treated as subordinate (cf. Gilbert, 2001; McGuire & Troisi, 1998), outgoing, sociable behaviors might be perceived (at least by themselves) as threatening to the status quo, ultimately to their safety and that of their families. These participants were not prepared to change their relatively subordinate position. Once again, lack of repertoires for dealing with the consequences of new sociability may be an adequate behavioral

explanation providing we set this in the context of evolution-determined patterns. It helps to remember that evolutionary mechanisms select for survival, not for "feeling good." Subordinates are more likely to remain part of a protective group and therefore survive, if they do not threaten dominants by manifesting outgoing behaviors. The possibility that meek, retiring behavior is hard-wired into some people would need to be corroborated by future studies. If it were, then clinicians would need to consider treatment goals such that continuing subordinate behavior is not pathologized but rather validated and shaped toward maximal quality of life. Those individuals who wish to change their position in the hierarchy, on the other hand, will need to tolerate and find ways to cope with the hostility of dominants.

Context and repertoires. Another effect of SSRIs that is seen as positive in one context is reduction in crying. For many who had been crying continuously—even when it "made no sense" to cry—prior to taking the medication, this effect is welcomed. But this is not an unmixed blessing. In fact, 20% of our sample complained of the loss of the ability to cry when it would have been appropriate: a family member or companion animal died and they could not cry, could not fully express the grief that belonged to the situation. Once again, the medication appears to stop the behaviors of suffering without allowing for appropriate response to situations—a de-contextualized, topographical rather than functional interpretation of "what is wrong" with depressed people. In this case, loss of repertoire (crying when aggrieved) conflicts with context: histories of social consequences shaping culturally determined "appropriate" behaviors in circumstances of bereavement.

We heard complaints that the SSRIs promoted complacency. Participants reported staying too long in a distressing job or relationship, overmuch compliance and lack of concern: the "happy robot" syndrome, as one participant termed it. People "stopped caring so much" about bad things that happened in jobs or relationships. Once again, the value of addressing symptoms outside of the context of their occurrence is problematic when those very symptoms have a place in other contexts. What might be happening here? Removing the ability to perceive an irritant—for instance by numbing the skin—may not be the most useful or appropriate way of dealing with the situation. Skin may be abraded or blistered severely if it is numbed while the organism remains in the environmental circumstance producing the irritation. Normally, if the skin were not numb, the organism would exit the situation if at all possible before serious damage is done. Analogously, staying in a distressing job or relationship because one "just doesn't care anymore" about what had irritated them before may look good on the surface. But it may not be an appropriate response to the whole situation. It depends on the relationship of the person and the situation. A Brer Rabbit story (Harris, 1880) may illustrate some of this complexity. Rabbit pleads with Fox not to throw him in the briar patch as a ploy to get the fox to do just that because the briar patch is Rabbit's home, an environment he knows thoroughly and wants to reenter. It might be useful for this character to numb himself to briars on his way to wiggling back to his accustomed pathways. On the other hand, numbing the skin of a frog and then tossing it into a briar patch might have unfortunate consequences even though the frog may not feel the hurt of the thorns. Thus, a briar patch may or may not be a bad situation—it depends.

Nesse (1998, 2000) hypothesized that depression may allow one to consider that a situation is not paying off, to detach from one's investment in it and prepare for alternatives. If indeed the situation called for such action, then medicating symptoms so that the distressed person cheerfully stays with the situation only sends good energy after bad because the situation is not optimal. By medicating symptoms out of context, we may be committing counter-therapeutic errors. Some of our participants reported that events at work or in a relationship that normally bothered them did not bother them in the least while they were taking medication—they just "did not care" anymore. This differs in function from the kind of detachment that allows one to move away from a major life endeavor such as career or relationship so as to embark on a new path. The price of this kind of detachment may well be considerable negative affect, unwillingness to eat, inability to sleep, as sense of not enjoying anything, etc. Depending on the complexity of the situation, such withdrawal may last a considerable length of time. Apparently we as clinicians need to be able to distinguish between situations where persevering would be beneficial in spite of current difficulties, and situations wherein persevering would be counterproductive. This would depend on the contingencies under which the person is operating. Consider the rat dropped into an inescapable container of water, is it more likely to survive to reproduce if it gives up sooner (saving some energy) on the off chance that a researcher may pick it out of the water (or in the wild, that the river current may bear it toward an overhanging branch or an outcropping of rock) or if it swims itself to exhaustion and then gets picked out or encounters a rock or branch? The former would save some energy toward a possible reproductive encounter, while the latter would not.

Psychiatrists are likely to respond with data showing that after 3 episodes, depression is no longer related to events in the patient's situation (Frank et al., 1996). However, "events" are usually defined narrowly, without considering socioeconomic background, cultural givens, or the cumulative effect of a lifetime of distressing situations. The context of the patient's situation still needs to be considered carefully.

Treatment implications

The adaptive functions of depressed behaviors mentioned in this chapter and the paradoxical reactions of our participants to SSRIs speak to the importance of well being rather than the simple absence of symptoms as goal of psychological treatment (cf. Fava 2002). In order to help patients achieve well being, clinicians need to assist them in working toward life goals, whether individual or communal. Since patients may not be aware of their goals (that is, the contingencies under which they are operating), especially if some of these goals are built in as survival mechanisms of the species, helping people discover or determine their goals may be a good deal of the work. There is evidence that activities perceived as furthering one's progress toward specific goals correlates with positive affect (Fleeson & Cantor, 1995), thus also potentially reducing a primary symptom of negative affect in depressive episodes. However to the extent that depressed behaviors themselves may be adaptive in various ways, discovering their function(s) in the person's life may be more important than simply stopping the symptoms.

Furthermore, whether personal or genetic, goals provide a context for the interpretation of symptoms and behaviors. This is a tenet of one form of radical behavioral therapy, Acceptance and Commitment Therapy (ACT) (Hayes, Wilson, & Strosahl, 1999). This direction of approach may even provide clinicians with a means to

undertake cross-cultural work without the problem of diagnostic inaccuracy—at least for the withdrawal behaviors. However the problems of cross-cultural communication are many, complex, and outside the scope of this paper.

The questions raised earlier about the use of medication may be answered (at least provisionally) from this recognition of the importance of context. For instance, now when we ask, "What would constitute 'getting better' for these people?" it is clearer that simply abolishing the list of depression symptoms does not necessarily equate with "getting better." True, we humans do not like feeling badly, sleeping poorly, being disinterested in socializing, food, sex and fun. But if there is something (or a number of things) wrong with the environment, the physical and social context in which we live, love, and work, stopping the discomfort at the bodily level may be less relevant than changing some aspect of the environment so that the body no longer responds with private aversive experience. "Getting better" may properly result only from a change in what is going on around the person: eliminating a stressful job condition, changing the people s/he associates with every day, increasing or decreasing the level of intimacy with which s/he interacts with certain people; or changing the individual's relationship with the same circumstances, such as decreasing expectations with respect to a job or relationship, and the like.

The principal question is the level or location of appropriate change: numb the skin so briar-patch thorns won't hurt? or move away from the briar patch? What are the individual's goals (what contingencies is s/he operating under)? Do they include gathering blackberries or staying in a thorn-protected environment safe from enemies? What are the possibilities of change available in the environment? This will help

determine the level and direction of change, a central clinical issue. There are some circumstances that shift only slowly. Even so, numbing ourselves to the irritation (or the deep wrongness, hurt, harmfulness) of a situation may not always work best.

The second question posed above, "How do we assess what 'getting worse' means if it is spoken of in terms of UPSEs and does not map onto the DSM symptom picture of depression or any other disorder?" now becomes intelligible in the context of goals (contingencies) and the value of well being. The third question, "Is 'depression' as described in the DSM what is actually wrong with them, or is this symptom list rather a set of epiphenomena?" now answers itself. And the fourth, "Could it be that treatment by medication is not relevant to what's really wrong with the suffering person in these cases?" similarly has been amply demonstrated in our sample of paradoxically dissatisfied participants. De-contextualization is one of the dangers of supposing that one (pharmacological) treatment fits all, in the case of emotional problems. However true it may be that a suffering person is feeling low, tired and unsociable, simply cheering and energizing them is clearly not always an appropriate answer.

Whether administering antidepressants under such conditions is itself adaptive or beneficial, or whether it's the right thing to do under the circumstances, is a difficult question. How long does it take to change the complexity of behavioral repertoires—to gain a renewed interest in human relationships or to find interest in a different line of work? What is the optimal point at which to begin exiting a withdrawal state and picking up the pieces of a broken life? We don't know a priori: the Skinnerian adage, "It depends" is relevant here. Just as there can be no single function for depression as a withdrawal syndrome, there can scarcely be a single optimal point in the development of

"depressive symptoms" or a single optimal length of time for making changes in one's life. Our society's attachment to the value of speed in all things: instant solutions, quick fixes—has yielded wonderfully fast-acting medications. But changing the symptoms has sometimes postponed the initiation of changes that people needed to make, and sometimes has made the quality of life worse in the sense that valued life goals (such as aesthetic appreciation, creative endeavor, empathic relating) became less accessible with medication than they had been even in a withdrawn state.

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Appendix A: The Psychological Side Effects Questionnaire (PSEQ)

PSEQdatascreen* *CONFIDENTIAL* SUB ID

DATE

DOB: __/__/__ Age: ____ M ___ F___

Flyer location:

Circle One: **Prozac** **Zoloft** **Paxil** **Luvox** **Celexa**

Did it work? Y ___ N ___
Take it again? Y ___ N ___
Who prescribed? GP__ Psychiatrist___ NP___ PA ___ Other:
Currently taking? Y ___ N ___ Which antidepr.?
_____

Did you decide to stop taking (med) on your own? Y___ N
With your doctor? Y ___ N ___
Did you finish your prescription? Y___ N ___

Permission for further contact? Y ___ N ____

NATIVE:
☐ Native American (please specify):
☐ Native Alaskan (please specify):
☐ Other Native (please specify):

AFRICAN:
☐ African (please specify):
☐ African-American
☐ Afro-Caribbean
☐ Other African (please specify):

LATINO/HISPANIC:
☐ Chicano/Mexican-American
☐ Puerto Rican
☐ Other Latino (please specify):

ASIAN:
☐ Chinese-American (please specify):
☐ Japanese-American
☐ Korean-American
☐ Vietnamese-American
☐ Indian-American [from India] (specify):

PACIFIC ISLANDER:
☐ Filipino (please specify):
☐ Hawaiian
☐ Samoan
☐ Other Pacific Islander (please specify):

CAUCASIAN:
☐ European-American (please specify):
☐ Middle-Eastern-American (specify):
☐ Other Caucasian (please specify):

☐ Other Asian (please specify):
☐ Chinese-American (please specify):

OTHER:
☐ (please specify):

Relationship/Marital status:

1. Single, not currently living with significant other
2. Currently living with significant other but not married
3. Married
4. Separated, not living with significant other
5. Separated, living with significant other
6. Divorced, not currently living with significant other
7. Divorced, currently living with significant other
8. Divorced, remarried
9. Widowed, not currently living with significant other
10. Widowed, currently living with significant other
11. Widowed, remarried

SMOKING
Packs per day_____
Pipe____ Cigar____ Chew____

ALCOHOL
Drinks per sitting ____ Times per week_____
OR per month_____ *OR* per year _____

COFFEE
Cups per day _____
OR per week _____

ASPIRIN OR SIMILAR PAIN-KILLER
(please specify):
Dose per time_____ Times per day _____
OR per week ____ *OR* per month _____

MARIJUANA OR OTHER MIND-ALTERING DRUG (PLEASE SPECIFY):
Amount _____ How often?_____

[Antidepressant dosage info.:]

Circle One: **Prozac** **Zoloft** **Paxil** **Luvox** **Celexa**

How much per day?

How long a period?

Did you ask your doctor for antidepr.? Or did your doc suggest that you take them?

What was happening in your life that led to this?

IN this section we're interested in the clinical symptoms of depression and how the medication affected them:

1. (Depressed) mood

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?
1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be
6 Unusually good mood

2. Could not enjoy things

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?
1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be
6 Extreme enjoyment

3. Sleep too much____ (check one)
too little ____

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?
1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be

(continued)

4. Appetite increase ____ (check one)
decrease ____

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?
1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be

5. Low self esteem

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?
1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be
6 Extremely high self esteem

6. Nervousness or agitation, had to pace or fidget

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?
1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be

(continued)

7. Being slowed down, couldn't move at normal speed

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?

1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be

8. Lack of energy, couldn't get going

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?

1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be
6 Better than ever—unusually energetic

9. Couldn't think or concentrate

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?

1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be
6 Could think or concentrate better than ever

(continued)

10. Couldn't make decisions, even about small things

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?

1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 Back to the way it should be
6 Decisions unusually easy: firm and quick

11. Thoughts of death or suicide

A *I had this symptom*
B *I did not have this symptom*
C *Only started bothering me after taking the medication*

After taking medication, how did this change?

1 Markedly worse
2 Somewhat worse
3 No help, no change
4 Somewhat better
5 No thoughts of death or suicide at all

***END OF SECTION:**
PROCEED TO NEXT

IN THIS SECTION we are interested in physical side effects you may have had, and if they affected your decision **to stop or not to take the medication again.**

SYMPTOM	√	3=not important 2=part of reason 1=the major reason for stopping or not doing again
headache	☐	
nausea	☐	
dizziness	☐	
tremor	☐	
twitching	☐	
sexual dysfunction	☐	
dry mouth	☐	
sleep (too much)	☐	
sleep (not enough)	☐	
other sleep problems	☐	
appetite decrease	☐	
appetite increase	☐	
constipation	☐	
diarrhea	☐	
nervousness/agitation	☐	
dental problems	☐	
ringing in the ears	☐	
sweating	☐	
other (please describe):	☐	

WHAT did your doctor tell you about potential side effects?

--about how long you should take the medication?

--about how long until it starts working?

DID you check in with your doctor periodically about how it was working?

(continued)

WERE there any other reasons for stopping your medication before using up your pills or not refilling your prescription?
For example, here are some practical reasons people sometimes give for not wishing to use medications:

- unknown long-term effects
- did not want to be dependent
- can't (don't want to) remember to take medication
- expense
- don't want to consume chemicals
- don't approve of drug companies
- want to solve my own problems
- other

Please explain. Anything you can tell us about your decision will be helpful.

IS THERE anything else about taking these medications that you would like us to know?

WOULD you be willing to give us permission to contact your prescriber about your dosage and the course of treatment?
DO you have their current address and/or phone number ?
IF SO, we will send you a consent form and release of information form to sign. [get name & mailing address on half-sheet]

[END OF PSEQ]

Appendix B: Manual and Coding Sheet for Unwanted Psychological Effects (UPSE)

PSEQ MANUAL

version 1B

Oct. 24, '01 (rev. 12/12/01; 2/08/02)

This is a project to document unintended effects of the Prozac family of antidepressants (also called SSRIs), namely Prozac, Zoloft, Paxil, Celexa, and Luvox. Unintended effects, that is, effects that have not yet been systematically documented in the literature.

What we will be doing is listening to recordings of confidential telephone interviews in which people report their experiences with these medications. The format is a semi-structured interview that gathers demographic data followed by questions about the subjects' use of substances both legal and illegal (e.g., tobacco, alcohol, caffeine, over-the-counter pain killers, and recreational drugs). Then we ask questions about the context of their use of SSRIs (e.g., did they ask for an antidepressant or did their doctor suggest it; what was happening in their life at the time, etc.).

All of this information is already recorded on our data sheets. You will be listening for and coding ***strange psychological effects*** experienced by the caller as a result of taking these drugs. What do I mean by strange psychological effects? Here are some examples:

- "I didn't feel like myself."
- "My father died and I couldn't cry."
- "I was a happy robot."
- "I became more social and out-going. People really liked it, but when I stopped
  taking Zoloft, I was just appalled by my behavior when I thought about it."
- "I felt like there was a wet rag over my life."
- "I had these Technicolor dreams—really vivid and strange, while I was on Zoloft.
  I liked them but they were intense and kind of exhausting."

There is a whole section of the interview that asks specifically about these effects, but that isn't the only place in the interview where these effects may be reported.

After the section that asks specifically about these effects, there is a long section inquiring into the person's experience of depressive symptoms ***both before and after*** taking the SSRI. Sometimes people elaborate on their stories as they report the effects of the drug on specific symptoms.

BE VERY SURE **THAT ANY STRANGE EFFECTS MENTIONED ARE DUE TO THE DRUG, NOT TO THE DEPRESSION ITSELF AND NOT DUE TO WITHDRAWAL EFFECTS.**

Following this section is a question about what ***physical*** side effects the caller experienced. These side effects are well-documented in the literature and are already recorded on our data sheets. But sometimes people also tell us about other strange effects in this section, and you will need to code these.

The next section of the interview asks about information the doctor provided when prescribing the medication. Then we ask about their reasons for stopping the medication and include practical reasons such as the expense or unknown long-term effects, etc. You do not need to code these as they are already marked on the data sheet. However, keep a sharp ear out for any further mention of ***strange psychological effects.***

TAKE *CONTEXT* INTO ACCOUNT, NOT JUST LITERAL WORDS.

CODING

Note: Items are in ALPHABETICAL ORDER *EXCEPT* "Empathy" and "Enjoyment," which are reversed (Enjoyment is #11; Empathy is #12). This was noticed too late to fix.

The PSEQ coding sheet is divided into two sections:

UNINTENDED EFFECTS and MISMATCH

Not every category of UNINTENDED EFFECT has a corresponding MISMATCH. This will become clearer as we proceed. First, let's look at an UNINTENDED EFFECT:

1. AFFECT (narrowed): This item refers to the person's ***experience of emotions***. The experience is reported as "a narrowed range of affect," often meaning that the deep, dark lows are gone—but so are the happy, excited, joyous highs. Sometimes the range of affect is so narrowed that the person feels no fluctuation in feeling at all—experienced as a kind of ***numbness*** or inability to feel their feelings. OR, the range can be narrowed to ***only*** highs or lows ***if*** the person senses that the rest of the range is ***missing***, not just that they can't access it. **NOTE: *The person does not have to say that they "don't like" this effect—they just have to report that they noticed it.***

   Some people report that they feel worse (more down, blue, bummed-out) *after* taking these antidepressants. This is certainly an "unintended effect." However, unless the *range* of feeling is narrowed (that is, you're sure the person was incapable of feeling happy or pleased or delighted because of the drug), do not code this as AFFECT (narrowed). This worsening of mood is already recorded on the data sheet as medication-induced depression.

1a. (*MISMATCH*) AFFECT ↑: Sometimes people report that only the lows were cut off in their experience, so that they felt only the highs or happy feelings. Doesn't this sound great? Many people think so—in fact, this might be the ideal function of an antidepressant drug, an "intended" effect. However, some people report that they ***didn't like the effect***. *(See next page)*

This would be coded as a MISMATCH. ***Be careful:***
NOT EVERYONE FEELS MISMATCH AT THE TIME THEY EXPERIENCE IT.

MISMATCH: subject disliked this effect (commonly expected to be a positive effect)
You will notice that there are three columns on the mismatch side: "while on," "after off," and "undiff." This is where you will code ***when*** the subject experienced a sense of MISMATCH.
If they noticed it while they were still on the drug, check "while on."
If they only felt the MISMATCH after getting off the drug, check "after off."
If you can't tell when they noticed it, check "undiff.," (= "undifferentiated").

2. AMBITION ↓: This item refers to an experience of decreased ambition, that is, lessened interest in and/or performance toward achievement, goal-oriented activity, and the like.

2a. (*MISMATCH*) PLEASURABLE, DANGEROUS *OR* GOAL-DIRECTED ACTIVITY ↑: Sometimes people report that under the influence of the medication they increased their activities (work-related, social or recreational). Because the symptom-picture of depression usually includes decreased activity (work-related, social or recreational), this would ordinarily be considered a good thing. But sometimes people report that they did not like the experience (either at the time or after stopping the medication). This would be coded as the MISMATCH item 3a: PLEASURABLE, DANGEROUS *OR* GOAL-DIRECTED ACTIVITY ↑

3. ANGER, IRRITABILITY ↑: This item refers to the experience of increased anger and irritability (impatience, touchiness, petulance, resentment, exasperation, indignation) due to the drug.

3a. (*MISMATCH*) ANGER, IRRITABILITY ↓: Sometimes people report that a lessening of irritability due to the drug was unpleasant to them for one reason or another. Weird, huh?

4. ANXIETY ↑: This item refers to an experience of increased cognitive apprehension, fear, worry, psychic tension, or uneasiness. ***NOTE:*** *do not include reports of "irritation" in this category. "Irritation" should be reported under* ANGER, IRRITABILITY ↑, *described below.*

5. APATHY, INDIFFERENCE ↑: This item refers to experiences of increased lack of interest or concern (about various areas of life) due to influence of the drug. This is often reported as, "just not caring." This lack clearly bothers the person as they report it. Another example might be a report that the person was INDIFFERENT to the impact of work or home situations on them even when that impact was negative. (That is, they stayed in a bad situation because of drug-

induced indifference.)

NOTE: APATHY, INDIFFERENCE ↑ *is different from* LETHARGY *(below).*
LETHARGY *refers to* <u>*physical*</u> *slowness, drowsiness, sluggishness, whereas* APATHY, INDIFFERENCE ↑ *refers to loss of interests or concerns about life.*

6. CONCENTRATION ↓: This item refers to experiences of reduced ability to attend to tasks at hand, such as reading, problem-solving, household chores, etc. <u>as a result of taking the antidepressant</u>.

6a. (*MISMATCH*) CONCENTRATION ↑: Sometimes people report an <u>increase</u> of ability to concentrate due to the influence of the drug, which is experienced as negative, in that it is "<u>over</u>-focused" or obsessively concentrated on one perception or activity. <u>This clearly bothers the person as they report it</u>.

7. CREATIVITY ↓: This item refers to experiences of reduced ability to engage in creative endeavors such as making music, writing stories or poetry, painting, humor, sculpting, etc. This should be a perception of <u>lost creative ability</u>, not merely indifference. AND this loss has to be <u>due to the drug</u>, not to depression.

7a. (*MISMATCH*) CREATIVITY ↑: Sometimes people report that an <u>increase</u> of creativity due to the drug was actually a negative thing (at least in retrospect, if not at the time).

8. CRYING ↑: This item refers to experiences of <u>unwanted</u> increased tearfulness due to the influence of the drug.

8a. (*MISMATCH*) CRYING ↓: Sometimes people report that a <u>decrease</u> of crying due to the drug (they had been crying too much due to depression before taking it) was <u>not</u> good
because they <u>could not</u> cry even when the situation called for it and they wanted to cry. Example: "My dad died, but I couldn't cry."

9. DISSOCIATION ↑: This item refers to a feeling of not being totally present to one's activities (due to the drug), as though watching oneself go through the motions of work, etc. (not necessarily a literal visual "watching").

10. DREAMS (vivid): This item refers to the experience of having unusually vivid, colorful, intense, memorable, or weird dreams, due to the drug.

11. ENJOYMENT, FUN ↓ (subjective sense): This item refers to loss of a sense of enjoyment or fun (laughter, spontaneity) due to the drug.

11a. (*MISMATCH*) ENJOYMENT, FUN ↑: Sometimes people report that an increased sense of enjoyment or fun (laughter, spontaneity) due to the drug was actually a negative thing (at least in retrospect, if not at the time).

12. EMPATHY ↓: This item refers to a loss of sensitivity to others; loss of ability to understand the feelings, thoughts, or attitudes of others, due to the drug. Do not count if the person has withdrawn from social interaction so there is no opportunity to have empathy.

13. LETHARGY ↑ (drugged, zombied): This item refers to feeling physically "drugged," or "zombied out" due to the drug. LETHARGY refers to physical slowness, drowsiness, or sluggishness.
NOTE: LETHARGY *is different from* APATHY, INDIFFERENCE ↑ *(above).* LETHARGY *refers to physical slowness, drowsiness, sluggishness, whereas* APATHY, INDIFFERENCE ↑ *refers to loss of interests or concerns about life.*

14. ME, MYSELF ↓: This item refers to a sense of not being oneself, due to the drug. Example: "I didn't feel like myself," "It just wasn't me."

15. MEMORY ↓: This item refers to an experience of problems with remembering, due to the drug.

16. OPINIONS (difficulty expressing): This item refers to difficulty expressing opinions, as a result of taking the drug.

16a. (*MISMATCH*) OPINIONS (ease expressing): Sometimes people report that the drug helped them to express their opinions more openly than usual. Ordinarily, we'd think of this as a good thing (assertiveness), but some people report that they didn't like the effect. Hence, this is a *MISMATCH.*

17. PROBLEMS (inability to work on): This item refers to the experience of being unable to work on one's problems (difficulties with self, family, work, career choice, etc.)—due to the drug. For example, inability to try to improve oneself, solve emotional difficulties, straighten out disagreements with others, accommodate to conflicting schedules, etc. in order to decrease distress.

18. SELF-CONFIDENCE ↓: This item refers to a loss of faith in one's own abilities, decisions, judgment, powers, etc., due to the drug.

18a. (*MISMATCH*) SELF-CONFIDENCE ↑: Sometimes people report that the drug gave them more self-confidence (sounds good!) but that they did not like the results, or in retrospect, they were embarrassed by their behavior.

19. SELF-ESTEEM ↓: This item refers to an experience of decreased respect for oneself, having a bad opinion of oneself (worse than before), due to the drug.

19a. (*MISMATCH*) SELF-ESTEEM ↑: Sometimes people report having a better opinion of oneself than before taking the drug—sometimes much better—and not liking it (usually in retrospect).

20. THOUGHTS, RACING: This item refers to an experience of speedy, out-of-control thinking, due to the drug.

21. OTHER (describe in margin): If you hear any unlisted ***strange psychological effect*** due to the medication, write it in the margin of the coding sheet (or on the back).

PSEQ CODING DATE _____ RATER INITIALS _____ SUBJECT ID #_____

	UNINTENDED EFFECTS		MISMATCH	while on	after off	undiff.
1.	AFFECT (narrowed)		1a. AFFECT ↑	1.		
2.	AMBITION ↓		2a. PLEASURABLE, DANGEROUS *OR* GOAL-DIRECTED ACTIVITY ↑	2.		
3.	ANGER, IRRITABILITY ↑		3a. ANGER, IRRITABILITY ↓	3.		
4.	ANXIETY ↑			4.		
5.	APATHY, INDIFFERENCE↑			5.		
6.	CONCENTRATION ↓		6a. CONCENTRATION ↑	6.		
7.	CREATIVITY ↓		7a. CREATIVITY ↑	7.		
8.	CRYING ↑		8a. CRYING ↓	8.		
9.	DISSOCIATION ↑			9.		
10.	DREAMS (vivid)			10.		
11.	(subjective sense) ENJOYMENT, FUN ↓		11a. ENJOYMENT, FUN ↑	11.		
12.	EMPATHY ↓			12.		
13.	*LETHARGY ↑ (drugged, zombied)			13.		
14.	ME, MYSELF ↓			14.		
15.	MEMORY ↓			15.		
16.	OPINIONS (DIFFICULTY expressing)		16a. OPINIONS (EASE expressing)	16.		
17.	PROBLEMS (inability to work on)			17.		
18.	SELF-CONFIDENCE ↓		18a. SELF-CONFIDENCE ↑	18.		
19.	SELF-ESTEEM ↓		19a. SELF-ESTEEM ↑	19.		
20.	THOUGHTS, RACING			20.		
21.	OTHER (describe in margin:)			21.		

*Note: Lethargy is entered under physical side effects in the database

Curriculum Vitae
Madelon Y. Bolling

Education:

2003	Ph.D. Clinical Psychology (expected) University of Washington, Seattle WA
1995	M.A. (Therapeutic Psychology) Seattle University, Seattle WA
1993-1994	Undergraduate studies in Psychology University of Washington, Seattle WA
1981	Ph.D. (Musicology) University of California, Santa Barbara CA
1976	M.A. (Music Performance) University of California, Santa Barbara CA
1968	B.A. (Summa cum Laude, Music) University of California, Santa Barbara CA

Research Experience:

2000-2002 Dissertation Research

Advisor: Robert J. Kohlenberg, Ph.D.

Psychological Side Effects Study (grant)

Author and advisor received a grant from the University of Washington's Royalty Research Fund to document and describe psychological side effects of SSRIs for depression.

Responsibilites: Designing & implementing a telephone survey study of individuals' experience of SSRIs taken for depression; planning & implementing recruitment; conducting recorded telephone interviews as approved by UW Human Subjects Review Committee; developing a survey instrument and conducting a content analysis of open-ended questions to obtain categories of formerly undocumented side effects; training interviewers, collaborators and coders; designing a database, overseeing data entry; data analysis and write-up.

1996-2000	Graduate Research Assistant Department of Psychology University of Washington
	FAP-Enhanced Cognitive Therapy for Depression Treatment Development Study
	Responsibilities: establishing and overseeing research protocols; coordinating subject recruitment; conducting phone screening, maintaining confidential address files and coded master list; enrolling subjects and serving as contact for subjects and therapists; conducting SCID-I & II and HRSD assessments; scheduling follow-up evaluations; conducting LIFE interview; supervising data tracking; coordinating annual updates for NIMH and UW Human Subjects Review Board; collaborating on grant writing and coordinating grant submissions to NIMH for the next stage of efficacy testing.
	Supervisor: Robert J. Kohlenberg, Ph.D.
1994-1995	Volunteer Research Assistant Department of Psychology University of Washington
	Supervisor: Chauncey Parker
	Responsibilities: collaborating with supervisor in drafting a treatment adherence measure for FAP-Enhanced Cognitive Therapy.
1993-1994	Undergraduate Research Assistant Department of Psychology University of Washington
	Supervisor: Kelly Koerner
	Responsibilities: learning to code therapist behavior in cognitive therapy sessions using the CSPRS adherence measure; reviewing and reporting on case conceptualization literature.

Clinical Experience

2002-2003	Internship: VA Puget Sound Health Care System American Lake Division Tacoma, WA Rotations: Mental Health Clinic; Addictions Treatment Center; Geriatric Research, Education, and Clinical Center
1997-2002	Staff Therapist (variable hours) Psychological Services and Training Center Department of Psychology University of Washington Responsibilities included providing individual therapy from four different theoretical bases for a diverse selection of clients with mood and anxiety disorders, performing intake assessments, personality assessments and referrals. Supervisors: Corey Fagan, Ph.D., Carol Henry, Ph.D., Janice Horike, Ph.D., Jane Simoni, Ph.D., Mavis Tsai, Ph.D.
2000-2001	Individual Outpatient Therapist (12 hrs/wk) University of Washington Student Counseling Center Responsibilities included history-taking; diagnosis; creating and following treatment plans, writing progress notes and reviews; keeping confidential records; case presentations; coordinating treatment by telephone and correspondence; crisis work with clients on telephone.
2000	Co-Leader of Group Treatment for Social Phobia Montlake Professional Building Seattle WA Supervisor: David Kosins, Ph.D.
1995-1996	Resource Coordinator Northshore School District and Eastside Mental Health Bothell WA Responsibilities included providing a variety of case management and supportive services to children, adolescents, parents and school personnel at several schools in the Northshore School District, through the Readiness to Learn Grant; assisting with tracking and program evaluation.

1995-1996 Individual Outpatient Therapist Extern
Eastside Mental Health
Bothell WA

Responsibilities included conducting semi-structured interviews at intake; diagnosis; creating and following treatment plans, writing progress notes and reviews; keeping confidential records; coordinating treatment by telephone and correspondence with medical, legal, and social agencies; crisis work with clients on telephone.

1994-1995 Individual Outpatient Therapist Intern
Eastside Mental Health at Bothell (see above)

1992-1993 Older Adult Services Volunteer
Seattle Mental Health Institute
Seattle WA

Responsibilities included interacting with chronically mentally ill geriatric clients living independently, through a day program promoting appropriate social interaction; taking notes for psychiatric consults; attending staff care meetings.

Teaching Experience in Psychology

2001-2002 Linked Writing Instructor (ENG 198/PSYCH 101)
Departments of English and Psychology
University of Washington

Responsibilities: Developing and teaching a psychology-focused freshman level course in critical academic thinking and writing.

1996-2001 Teaching Assistant
Department of Psychology
University of Washington

(Intro to Psychology, Abnormal Psychology, Personality, Intro to Statistics for Behavioral Sciences, Clinical Psychology [substitute teaching], Behavior Change [graduate seminar, substitute teaching])

Publications In Psychology

Bolling, M. Y. (2003). Research and Representation: A Conundrum for Behavior Analysts. *Behavior and Social Issues, 12*: 19-28.

Bolling, M. Y., Parker, C. R., Kanter, J. W., Kohlenberg, R. J., and Tsai, M. (in press). The client-therapist interaction: The core of a behavioral approach. In Sulz, S. (Ed.), *Familie und Verhalten: kognitiv-behaviorale Familientherapie.* Munchen: CIP-Medien.

Kohlenberg, R.J., Bolling, M.Y., Kanter, J.W., & Parker, C. R. (2002). Clinical behavior analysis: Where it went wrong, how it was made good again, and why its future is so bright. *Behavior Analyst Today,3*: 248-253.

Kohlenberg, R. J., Kanter, J. W., Bolling, M. Y., Parker, C. R., and Tsai, M. (2002). Enhancing Cognitive Therapy for depression with Functional Analytic Psychotherapy: Treatment guidelines and empirical findings. *Cognitive and Behavioral Practice 9*:213-229.

Kohlenberg, R. J., Tsai, M., Parker, C. R., Bolling, M. Y., and Kanter, J. W. (2000). Focusing on the client-therapist interaction. *European Psychotherapy, 1*:21-29.

Bolling, M. Y., Kohlenberg, R. J., & Parker, C. R. (2000) Behavior analysis and depression. Chapter 6 (pp. 127-152). In Dougher, M. J. (Ed.). *Clinical behavior analysis.* Reno: Context Press.

Parker, C. R., Bolling, M. Y. & Kohlenberg, R. J. (1998). Operant theory of personality. Chapter 7 (pp. 155-171). In D. Barone, M. Hersen, and V. B. Van Hasselt (Eds.) *Advanced Personality.* New York: Plenum Press.

Bolling, M. Y. (1995). Acceptance and Dasein. *Humanistic Psychologist, 23*, 213-226.

Presentations

Kohlenberg, R. J., Kanter, J. W., Bolling, M. Y., Parker, C. R., Wexner, R., & Terry, C. M. (May 2002). *FECT: A Behavioral Treatment for Depression.* .Workshop presented at the 28th Annual Convention of Association for Behavior Analysis (ABA), Toronto, Ontario, CAN.

Bolling, M. Y. (May, 2002). A paradox in successful pharmacological treatment. In R. Wexner (Chair), *Behaviorists in Foreign Territory:A Functional Analytic Look at Treatment as Usual.* Symposium presented at the 28th Annual Convention of Association for Behavior Analysis (ABA), Toronto, Ontario, CAN.

Bolling, M.Y., Kanter, J. W., Wexner, R., & Kohlenberg., R. J. (July, 2001). Developing FECT: Study overview and outcomes at post-treatment and three months. In M. Y. Bolling (Chair), *A Behavior Analytically Informed Treatment for Depression.* Symposium presented at the World Congress of Behavioral and Cognitive Therapies Vancouver, B.C., Canada.

Bolling, M. Y. (May, 2001). Research and representation: A conundrum for behavior analysts. In M. R. Ruiz (Chair), *Behavior Analysis and Cultural Differences*. Paper Session presented at the 27th Annual Convention of Association for Behavior Analysis (ABA), New Orleans, LA.

Kohlenberg, R. J., Bolling, M. Y., Kanter, J. W., Parker, C. R., & Wexner, R. (May 2001). *FECT: A Behavioral Treatment for Depression.* Workshop presented at the 27th Annual Convention of Association for Behavior Analysis (ABA), New Orleans, LA.

Bolling, M.Y. (Chair), Kohlenberg, R. J., Armstrong, B. K., Griffee, K., & Augustson, E. M. (May, 2001). (*Thirty sessions with a difficult FECT research client.)* Clinical Roundtable presented at the 27th Annual Convention of Association for Behavior Analysis (ABA), New Orleans, LA.

Bolling, M. Y., Kanter, J. W., Parker, C. R., & Kohlenberg, R. J. (May, 2001). Developing FECT: Study overview and outcomes at post-treatment and three months. In M. Y. Bolling (Chair), *A Behavior-Analytically Informed Treatment for Depression.* Symposium presented at the 27th Annual Convention of Association for Behavior Analysis (ABA), New Orleans, LA.

Kohlenberg, R. J., Bolling, M. Y., Parker, C. R., & Kanter, J. W. (May, 2000). *FECT: A Behavioral Treatment for Depression.* Workshop presented at the 26th Annual Convention of Association for Behavior Analysis (ABA), Washington, DC.

Bolling, M.Y., & Kohlenberg., R. J. (May, 2000). Depressive dis-ease: Disorder in the medical model. In M. Y. Bolling (Chair), *Functional Analytic Perspectives on Depression: What's Different?* Symposium presented at the 26th Annual Convention of Association for Behavior Analysis (ABA), Washington, DC.

Kohlenberg, R. J., Bolling, M. Y., Parker, C. R., & Kanter, J. W. (May, 1999). *Functional Analytic Psychotherapy (FAP) enhanced Cognitive Therapy (FECT): Emphasizing the Client-Therapist Relationship in Cognitive Therapy.* Workshop presented at the 25th Annual Convention of Association for Behavior Analysis (ABA), Chicago, IL.

Kohlenberg, R. J., Parker, C. R. & Bolling, M. Y. (1997, May). *Cognitive Therapy for Depression: A Behavioral Approach.* Workshop presented at the 23rd annual convention for the Association for Behavior Analysis (ABA), Chicago, IL.

Parker, C. R., Bolling, M. Kohlenberg, R. J., Beitz, K. K. & Hord, N. (1997, May). Therapist in-vivo strategies scale: a measure of the therapist's focus on the therapeutic relationship.

Poster presented at the 23rd annual convention for the Association for Behavior Analysis (ABA), Chicago, IL.

Bolling, M., Parker, C. R., & Kohlenberg, R. J.(1996, October). An introduction to Functional Analytic Psychotherapy (FAP). In C. R. Parker (Chair), *Relationship-Centered Psychotherapy: A Skinnerian Based Approach.* Symposium presented at the annual convention of Northwestern Association for Behavior Analysis (NWABA), Ellensberg, WA.

Grant Experience:

Assisted in preparation of proposals:

Kohlenberg, R. J., Principal Investigator. (March, 2000). *Subtle Psychological Side Effects: Refining our Understanding of Depression.* Proposal to Royalty Research Fund, University of Washington. Approved for 9/00 – 9/01 (unfunded extension to 9/02).

Kohlenberg, R. J., Principal Investigator. (May, 2000) *Subtle Psychological Side Effects: An Adherence Factor?* Grant proposal to National Institute of Mental Health. In revision.

Kohlenberg, R. J., Principal Investigator, Dunner, D., MD, Collaborating Investigator, Hollon, S. PhD, Collaborating Investigator. (Oct. 2000; Oct. 2001; July 2002) *Enhancing Cognitive Therapy for Depression.* Grant proposal & revisions submitted to National Institute of Mental Health.

Kohlenberg, R. J., Principal Investigator. (Sept. 1996; May, 1997). *Enhanced Cognitive Therapy for Depression.* National Institute of Mental Health Grant #MH53933.

Professional Organizations:

Association for Behavior Analysis (Clinical, Family, Behavioral Medicine SIG; Community Interventions, Social & Ethical Issues SIG)
Association for Advancement of Behavior Therapy
Association for Women in Psychology

Current Certificate: State of Washington Registered Counselor # RC00025501