

**Additional file 2** - Historical trends in prescription drug usage in the United States that can impact drug of abuse testing

## **Challenges and limitations of routine immunoassay-based drug of abuse screening used in emergency medicine**

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### **Background**

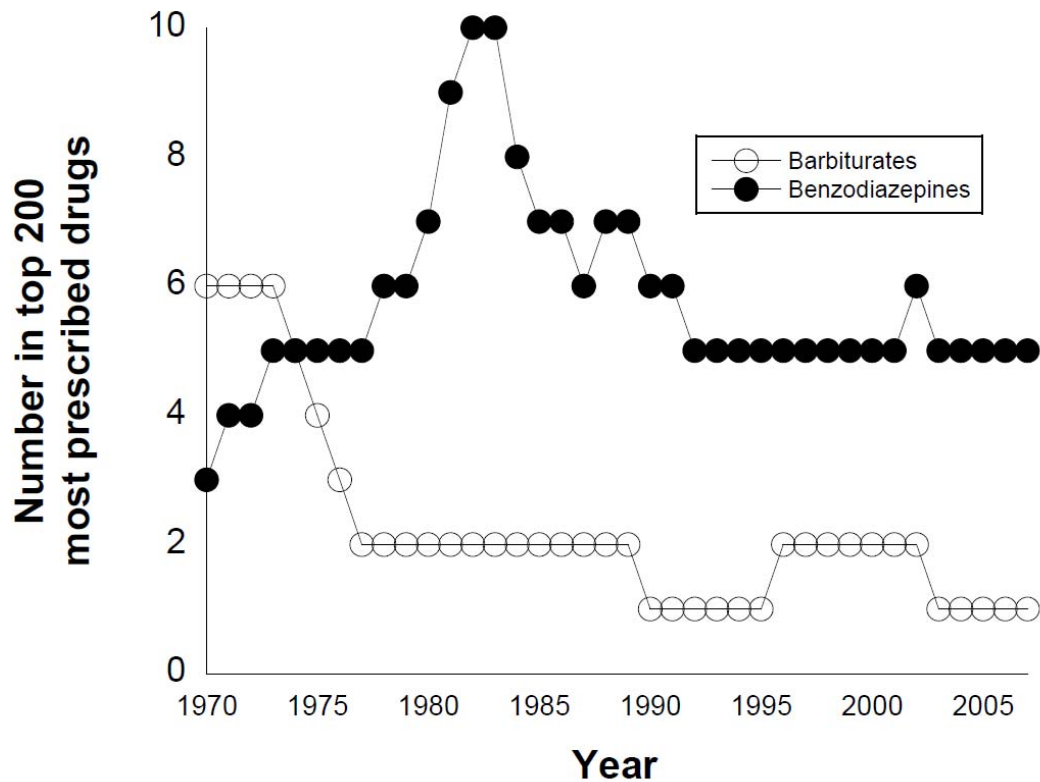
Information on prescription drug utilization in the United States in the time period from 1970-2007 is scattered in a number of different publications that present and organize the data in various formats [1-38]. We compiled and analyzed this data focusing on amphetamines, antidepressants, antipsychotics, barbiturates, benzodiazepines, other sedative/hypnotic/anxiolytic drugs, and opioids. Until 1997, the prescription drugs were ranked by number of prescriptions, but the actual volumes were not provided. Therefore, for comparisons across the time period from 1970 to 2007, we simply compared whether drugs were in the top 200 most prescribed drugs. From 1998-2007 [28-38], the data for numbers of prescriptions were provided, allowing for more detailed comparisons. To make the data more relevant to our study, the total number of dispensed prescriptions containing an active drug were determined, combining generic and branded formulations

of the same drug. For combination medications (e.g., hydrocodone/acetaminophen), each active product was counted separately as a drug. This analysis provides a measure of total exposure to drugs. The sorted data for 2007 is found in Additional file 1, tab T.

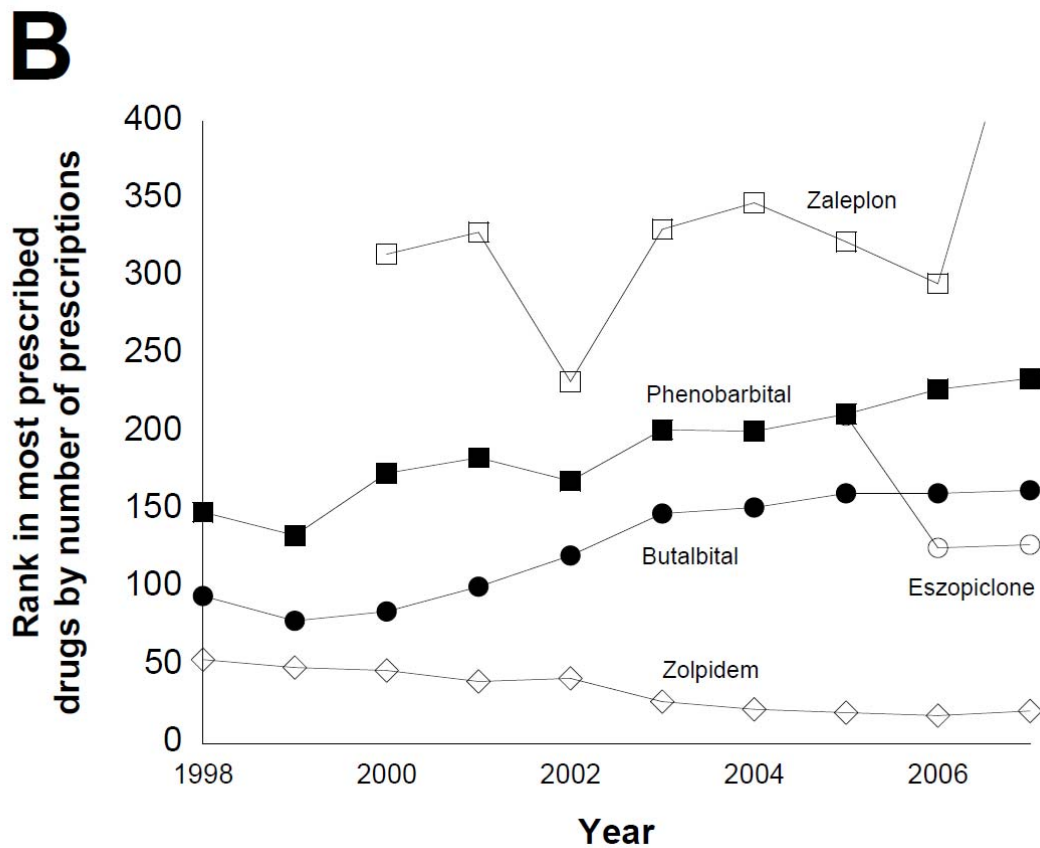
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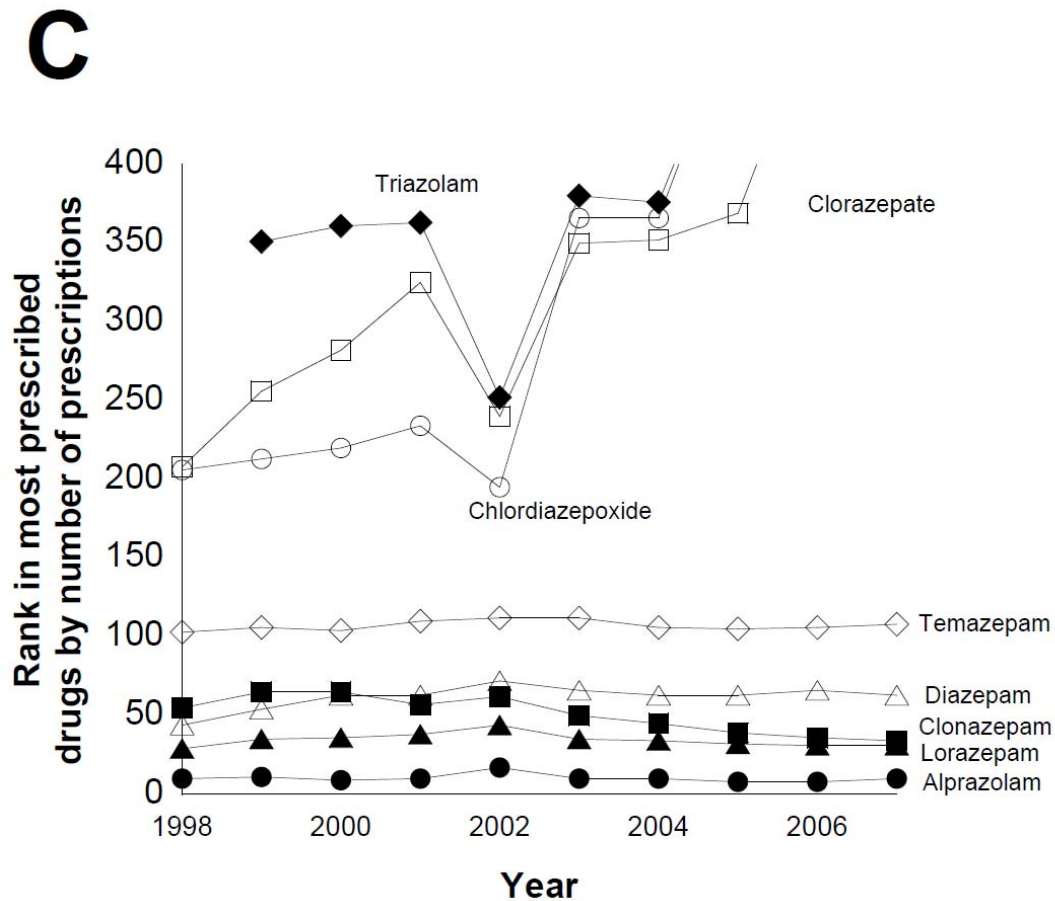
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**A**

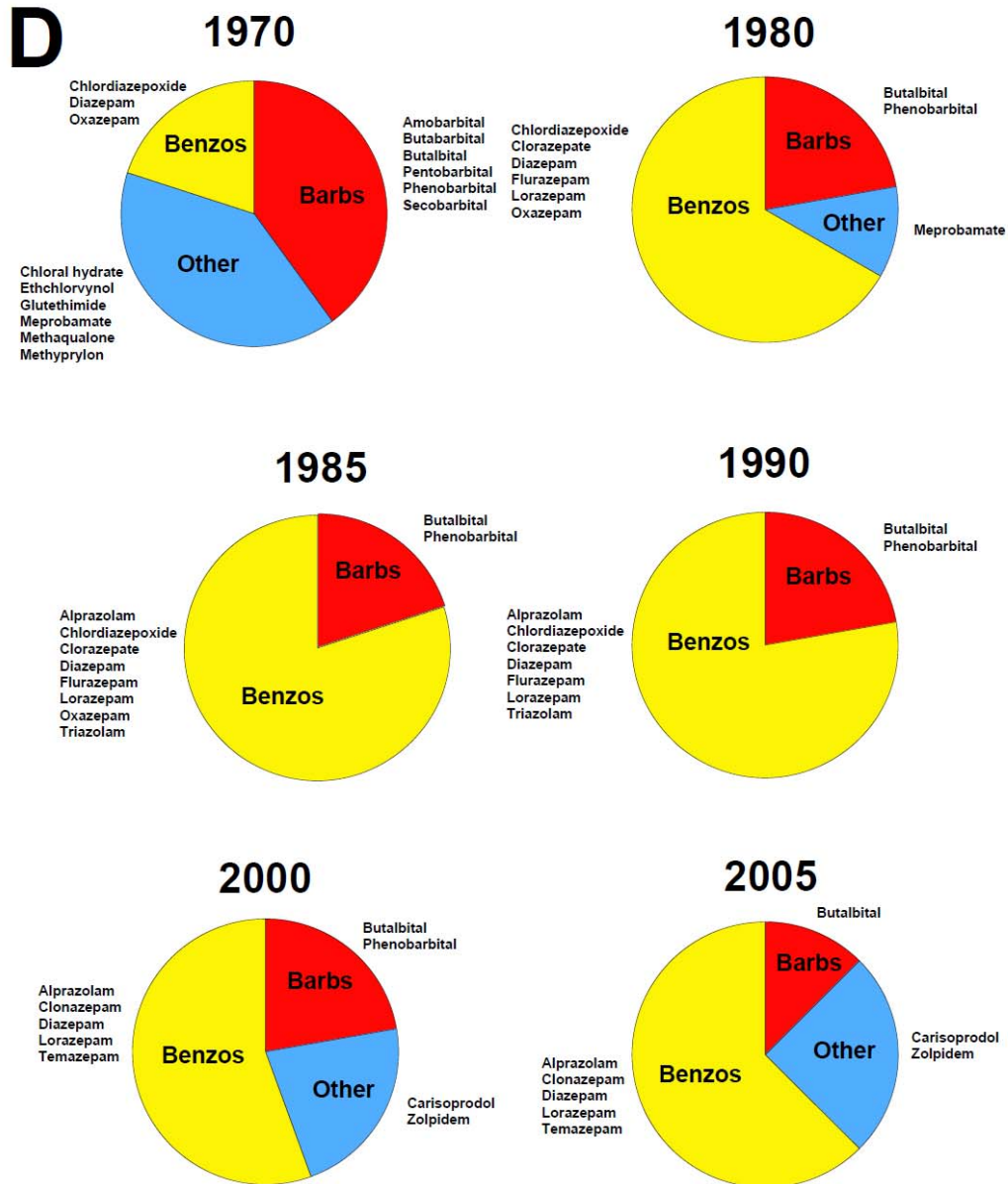
**Figure S2-A.** Number of barbiturates and benzodiazepines among the top 200 most prescribed medications in the United States in the time period from 1970 to 2007. The barbiturates were the dominant sedative/hypnotics until the mid-1970s but were then displaced by benzodiazepines. Currently, only one barbiturate (butalbital, found in various combination products) is in the top 200 most prescribed medications.



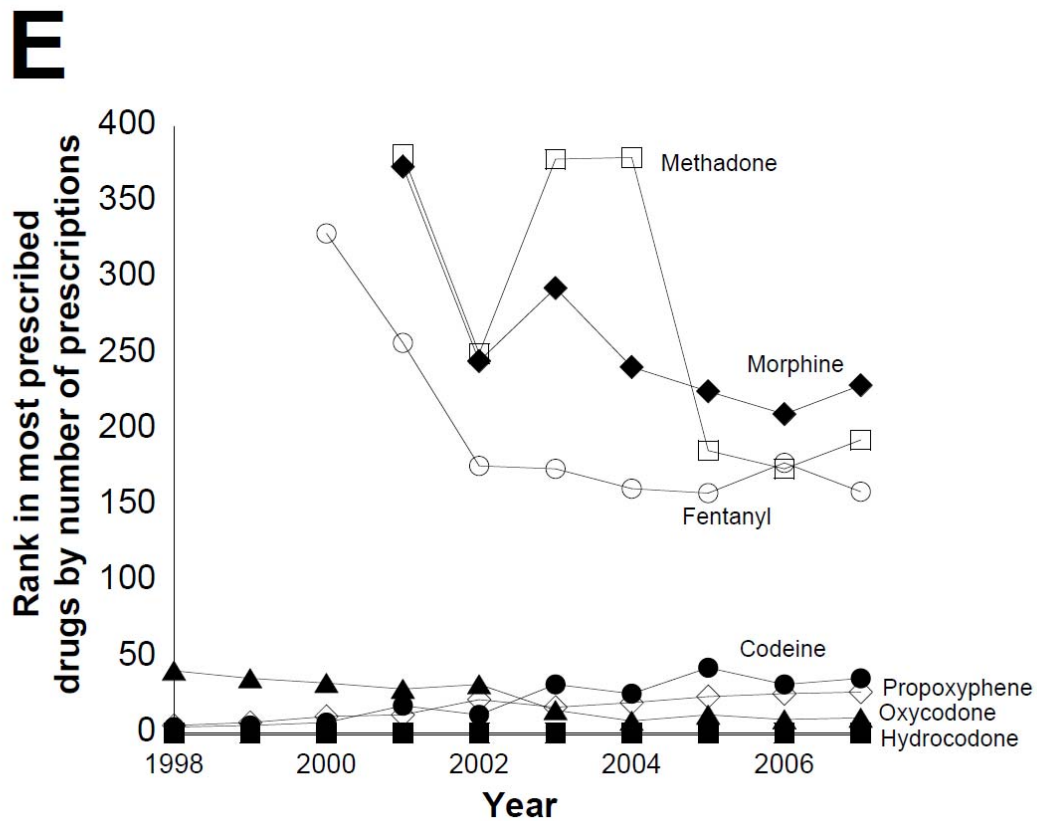
**Figure S2-B.** Rank of two barbiturate (●, ■) and three non-barbiturate/non-benzodiazepine hypnotic medications (○, ◇, □) by total number of prescriptions in the United States in the time period from 1998-2007. In the last decade, prescriptions for butalbital and phenobarbital have been steadily declining, while prescriptions for eszopiclone and zolpidem (two drugs not detected by any currently marketed DOA/Tox immunoassay screen) are increasing.



**Figure S2-C.** Rank of benzodiazepine medications by total number of prescriptions in the United States in the time period from 1998-2007. Prescriptions for chlordiazepoxide, clorazepate, and triazolam have declined to the point that these drugs are no longer ranked in the top 400 most prescribed medications. Prescriptions for five other benzodiazepine medications (alprazolam, clonazepam, diazepam, lorazepam, and temazepam) have been relatively steady over the last decade. ‘Classic’ benzodiazepines that share metabolites with diazepam (and are generally best detected by currently marketed benzodiazepine screening immunoassays) are indicated by open symbols. All other benzodiazepines are indicated by closed symbols.

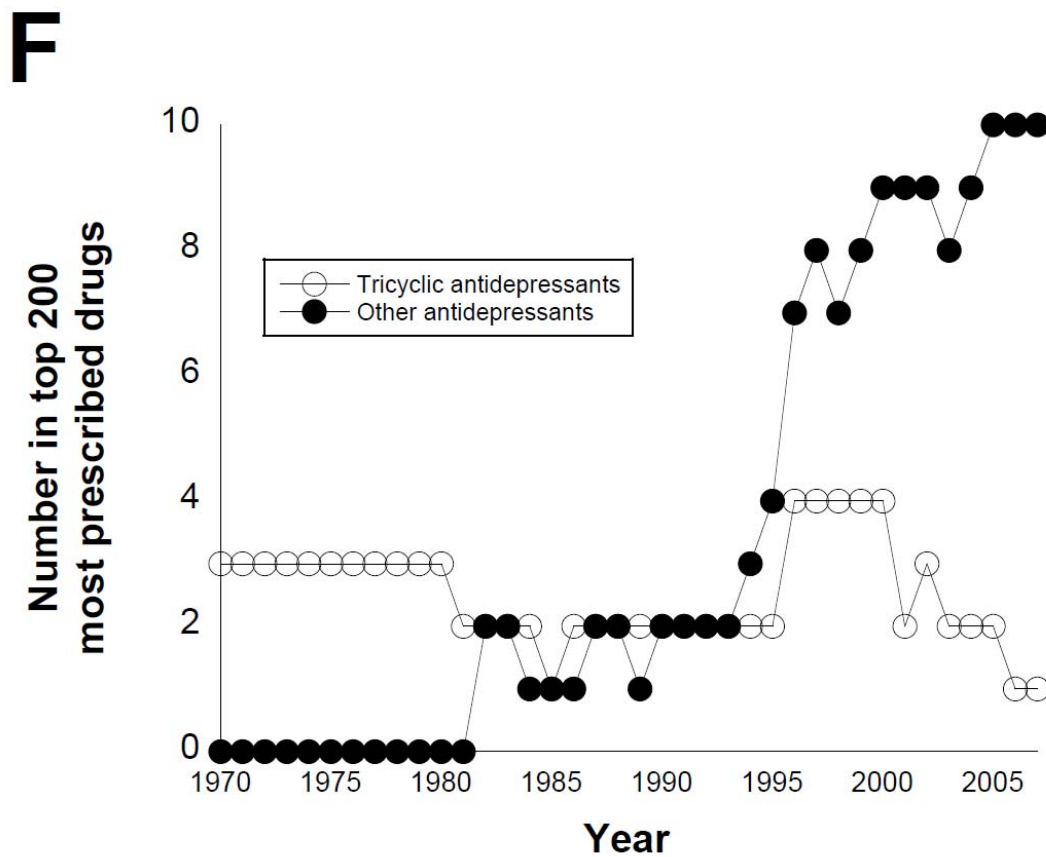


**Figure S2-D.** Shifts in number of prescriptions for barbiturate, benzodiazepine, and other sedative/hypnotic/anxiolytic medications in the United States in the time period from 1970-2007. The pie charts indicate number of drugs in each of three categories – barbiturates (barbs), benzodiazepines (benzos), and other – that were ranked in the top 200 most prescribed medications in six different years.

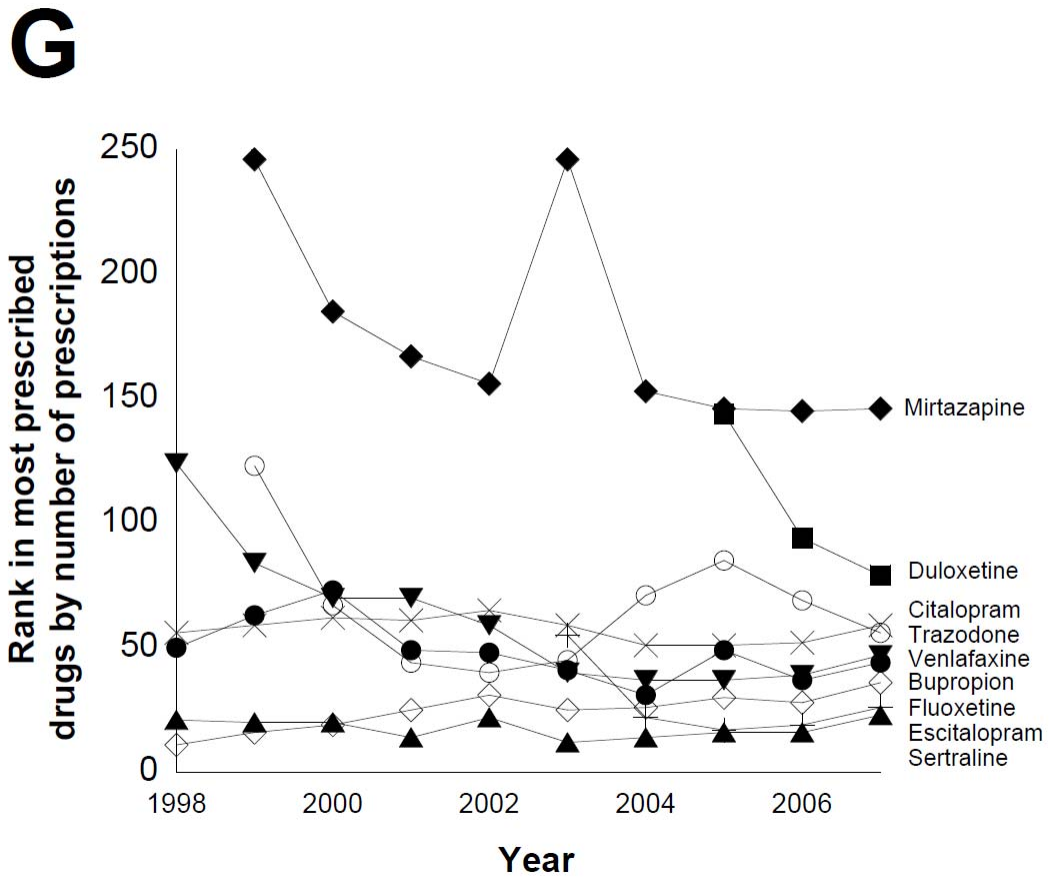


**Figure S2-E.** Rank of opioid medications by total number of prescriptions in the United States in the time period from 1998-2007. Opiates are indicated by closed symbols. Non-opiate opioids (fentanyl, methadone, and propoxyphene) are indicated by open symbols. Prescriptions for codeine, hydrocodone, and oxycodone have remained in the top 50 most prescribed medications and relatively steady in number over the last decade. Prescriptions for fentanyl, methadone, and morphine have increased in number during the last seven years.

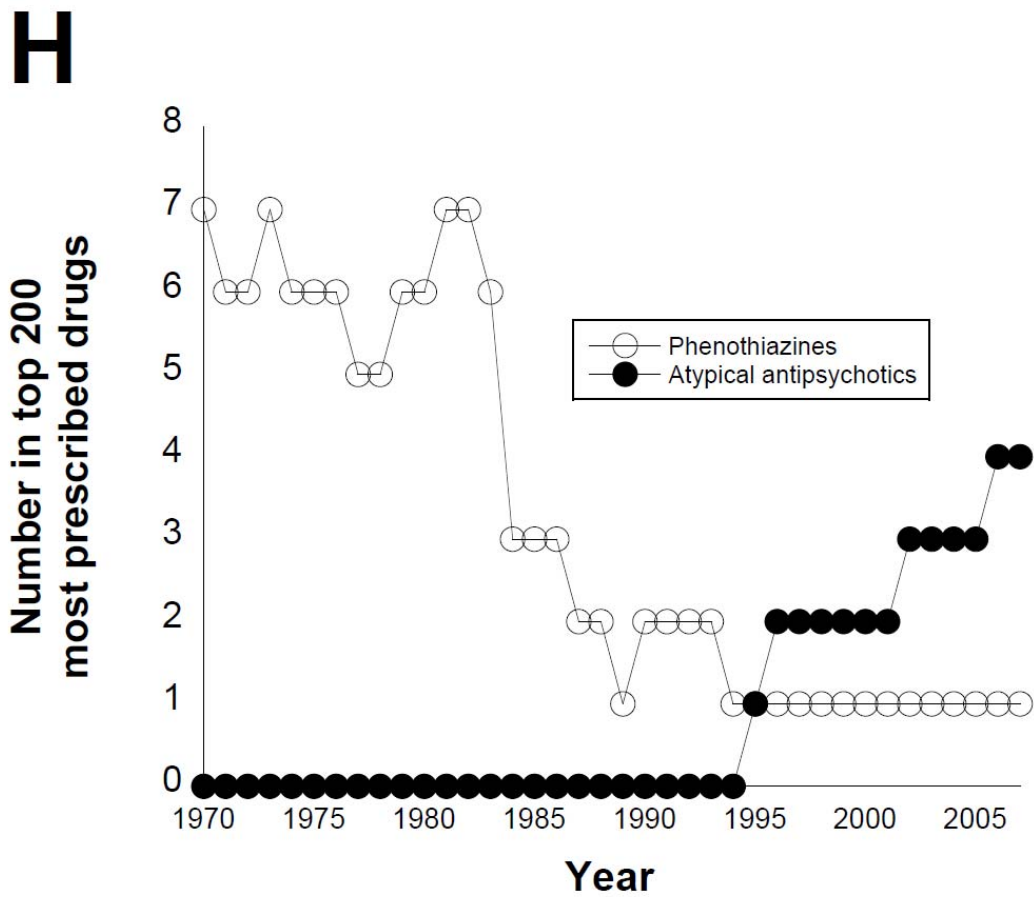




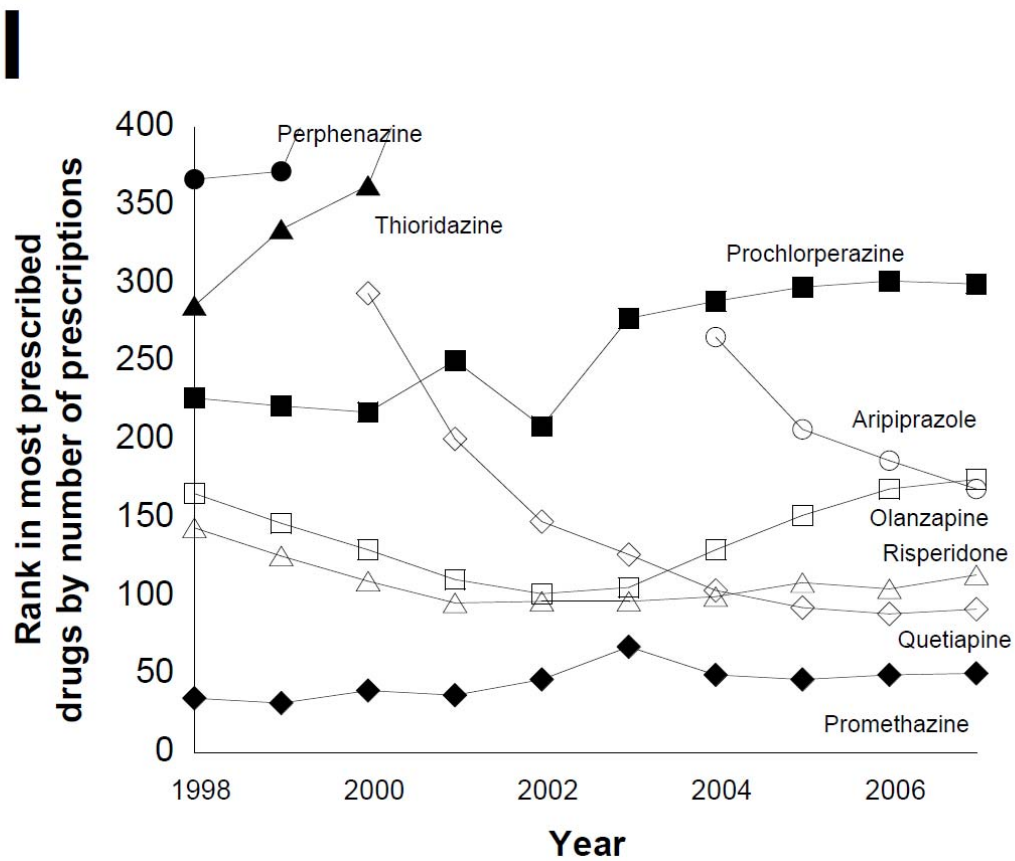
**Figure S2-F.** Number of antidepressants among the top 200 most prescribed medications in the United States in the time period from 1970-2007. The antidepressants are divided into two broad categories: tricyclic antidepressants (○, includes amitriptyline, desipramine, doxepin, imipramine, and nortriptyline) and other antidepressants (●, includes selective serotonin reuptake inhibitors, serotonin-norepinephrine inhibitors, bupropion, and trazodone). Currently, only one tricyclic antidepressant (amitriptyline) is in the top 200 most prescribed medications in the United States. Cyclobenzaprine, commonly prescribed as a muscle relaxant, was not included as a tricyclic antidepressant for this figure, although this drug is structurally very closely related to amitriptyline and other tricyclic antidepressants.



**Figure S2-G.** Rank of non-tricyclic antidepressant medications by total number of prescriptions in the United States in the time period from 1998-2007. Eight of these antidepressant medications rank in the top 80 most prescribed medications. A similar plot that includes tricyclic antidepressants is found in the main body of the manuscript (Figure 5A).



**Figure S2-H.** Number of antipsychotics among the top 200 most prescribed medications in the United States in the time period from 1970-2007. The antipsychotics are divided into two broad categories: phenothiazines (○, includes a variety of drugs such as chlorpromazine, thioridazine, and trifluoperazine) and atypical antipsychotics (●, includes aripiprazole, clozapine, olanzapine, quetiapine, and risperidone). Note that some phenothiazines, particularly prochlorperazine and promethazine, are likely most widely used for indications other than psychotic illness.



**Figure S2-I.** Rank of antipsychotic medications by total number of prescriptions in the United States in the time period from 1998-2007. Phenothiazines are indicated by closed symbols. Atypical antipsychotics are represented by open symbols. Prescriptions for atypical antipsychotics over the last decade have been steadily increasing to the point that four of these drugs are among the top 200 most prescribed medications. There is only one phenothiazine left in the top 200 most prescribed medications (promethazine, formulated either alone or in combination with other drugs).