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Medication Adherence and Compliance: Uncontrolled Variables in Psychiatric Clinical Drug Trials

Philip Corrado[1], Linka Griswold[2]*, Joan Murray[2]*

[1]*Director of Behavioral Medicine Services, Pasadena Rehabilitation Institute, USA*

*[2]*Doctoral Candidate at the California School of Forensic Studies, Alliant International University, Los Angeles*

*[2]*California School of Professional Psychology, Alliant International University, Los Angeles*

Abstract

Over the past decade, there have been thousands of controlled clinical trials assessing the efficacy and safety of drugs used to treat a range of illnesses. The purpose of this review is to document how often medication adherence is controlled in pharmaceutical drug research. Authors of this study focused specifically on psychiatric drugs and clinical drug trials between the years 2002 and 2012. The automated searches included the use of search engines designed to scan documents for key words; limiters were set to narrow the search queries to human subjects, clinical drug trials, and publications within the past 10 years (2002 to 2012). Databases reviewed included: PubMed / Medline, Science Direct, Scirus, and Scopus. The variable, control for adherence, occurred in a low frequency among articles published, and statistical significance was found between drug classes as well as queried search phrases that examined adherence versus compliance. Overall, mention of control for adherence or compliance is missing in a significant and large portion of published articles involving clinical drug trials. The results revealed that the majority of articles written, across all four databases and all seven drug categories, did not control for medication adherence and compliance. At the conservative end, results show that approximately 67% of articles on clinical drug trials neglected to mention or control for compliance. Results call into question the validity of clinical drug trial claims, as well as the safety and efficacy of pharmaceuticals in psychiatric practice.

Introduction

In a recent study, Gottlieb, Corrado and Griswold identified the lack of control for adherence and non-compliance to drugs as serious impediments to clinical drug studies [1]. These authors concluded that the lack of control for adherence compromises the safety of patient populations for which specific drugs are tailored. Gottlieb and colleagues focused on four drug categories: antidepressants, antihypertensives, antivirals, and analgesics. Their results raise concerns regarding the lack of measurement of adherence and compliance in clinical drug studies. They showed that the majority of published drug studies over the last 12 years neglected to control for medication adherence. They also noted that, "…despite the current FDA regulations (1997) on clinical drug trials, which mandate the investigator to monitor patient adherence to the treatment regimen, there is a low percentage of studies that even attempted to address the issue of adherence" [1]. According to Gottlieb et al. [1] among the publications that addressed adherence, some merely mentioned adherence without any attempt to control for it. Gottlieb et al. also conducted both manual and automated searches and compared the hit rates of the two procedures. The automated and manual search of studies yielded different results (3%-9% vs. 15.2%, respectively); however, the overall frequency of publications in which adherence was mentioned was extremely low under either search method.

In consideration of the fact that Gottlieb et al. focused on only four drug classes and used specific databases, this study is designed to build and improve upon the former with a more exhaustive use of databases, tailored for the health sciences. Secondly, the present study included seven psychiatric drug categories: antidepressants, antipsychotics, anticonvulsants, anxiolytics, stimulants, opioids, and mood stabilizers. Although the Gottlieb et al. study showed that the majority of clinical drug trials do not control for adherence and provided valuable insight into pharmacological safety, the study had serious limitations. For example, their publication lacked advance statistical analyses, neglected to include tables or graphs, and showed inconsistencies in search phrases and limiters applied to the queries. Lastly, their study neglected databases that may contain articles pertinent to psychiatric drug research such as Scirus or Scopus.

In order to mitigate the limitations of the former study, more thorough and multilevel analyses were attempted in the present study. One caveat, the present authors refrained from manual searches and focused exclusively on automated searches.

Before examining the results of this present study, a quick review of some of the factors that influence non-adherence and non-compliance will be provided. Patient variables such as cognitive factors, disease progression, side effect profiles, drug interactions and therapeutic alliance are among many that confound and complicate the measurement of medication adherence (D. Turk, personal communication, March 2011) [1].

First, a review of the terms *adherence* and *compliance* is appropriate. The terms *adherence* and *compliance*, although sometimes defined in different ways, are used interchangeably in the literature reviewed. Treatment adherence is defined as the extent to which a person's behavior coincides with medical or mental health advice. Adherence suggests an active patient role: a willingness to participate. Adherence also implies consistency with a prescribed regimen; it is analogous to joining or attaching oneself to something. In contrast, the term compliance

***Corresponding author:** Linka Griswold, 26500 West Agoura Rd, Suite 102-413, Calabasas, CA 91302, Tel: 310-570-9927; E-mail: Linka.Griswold@att.net

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implies a more passive patient role. Compliance characterizes the patient as acquiescing, resigning or relinquishing authority to another [2]. The latter point becomes more salient when comparing the hit rate percentages between the key search words, adherence vs. compliance, in the scientific literature. It can lead to conjectures and discussions on how prescribers view patients.

Non-adherence to treatment recommendations was estimated at 40%, with some studies showing that it may be as high as 75%; an average non-adherence rate was estimated at about 50% [3-5]. Turk approximated that 67% of patients receiving new written prescriptions each year will show either partial or complete non-compliance [6]. A review of the World Health Organization (WHO) publications revealed that 50% of patients diagnosed with chronic disease adhered to recommended treatments; the implications of this finding include the fact that nearly half of medication treatment recipients do not adhere or comply with medication protocols. Undoubtedly, such statistics warrant more research and demand attention to the efficacy and safety of pharmaceuticals [7].

Other studies confirm the low adherence trends involving synthetic antidepressants. According to Ellen et al. [8] as many as 50% of clinical drug trial participants drop out or cease medication after 3 months. Such a high mortality rate in clinical research is problematic and confounds the generalizability of statistical findings. One might also infer that pathology and severity of illness modulate adherence rates. As an example, Miklowitz and Johnson [9] showed that nearly 60% of patients diagnosed with bipolar disorder discontinue treatment within the first year Lack of adherence in patients with BD may be related both to the side effect profiles of drugs and to the symptoms of the disorder. In fact, past studies have shown patients with BD show similar, low levels of non-adherence and poor compliance [10].

Patient-centered variables

It is reasonable to foresee that as drug dosages increase, treatment adherence decreases [4]. These findings suggest that more frequent dosing corresponds to less patient adherence. Cognitive variables such as a patient's locus of control with regard to treatment adherence should be evaluated. As stated by Gottlieb et al., non-adherence could be a function of factors such as perceived or real decreases in disease progression or symptomatology, perceived helplessness, defense mechanisms such as denial, motivational apathy, and lack of family or financial support. Patients have been known to alter their medication-taking patterns based on a "feel good" rate or "wisdom of the body" rule; some stop their medication intake all together after experiencing symptomatic relief [1,2].

Studies have shown a correlation between dosage frequency and drug compliance; with higher dosages negatively correlated to rates of compliance [11]. A patient's perception of drug efficacy and side effects also correlate strongly with lack of adherence [2]. In one study, Zhang et al. found that patients diagnosed with schizophrenia and provided augmentation with natural / homeopathic remedies, in conjunction with antipsychotics, showed markedly improved rates of adherence as compared to the non-augmented medication group. A similar finding was uncovered when patients with BD given only pharmacotherapy were compared to patients provided pharmacotherapy and psychotherapy combined. Patients in the latter group had higher rates of adherence [12].

In the drug classes of anxiolytics and opioids, and arguably stimulants, lack of adherence may be characterized by over-medicating as opposed to under-medicating. Opioids naturally run the risk of addiction in vulnerable patient populations [13]. Many pain patients experience common phenomena such as drug tolerance or dependence. These are also typical signs of early drug addiction [14]. The strong psychological components that add to the phenomena of addiction are important in learning how to unravel the mind-body connection; especially, when pharmaceuticals are involved [13]. Anxiolytics like the benzodiazepines and stimulants, such as those prescribed for the treatment of ADHD, are often abused and pose both legal and ethical problems for patients and their prescribers. Cognitive factors are difficult to quantify but important in considering adherence or non-adherence behavior. More detailed examination of psychological variables may help scientists develop evidence-based programs to increase medication adherence / compliance.

Psychological reactance, a cognitive phenomenon, plays a role in whether patients collaborate or behave as passive spectators in their medical care [15]. When patients feel usurped by the physician regarding their treatment plan, the patient's commitment to treatment adherence weakens. Likely, this extends to the patients' view of the therapeutic alliance as well. Patients are not as willing to adhere to their medical regimen when they are not given an opportunity to actively participate in decision making [15-17]. Patient Controlled Anesthesia (self-administering of pain medications) illustrates the phenomenon. Patients allowed control over their medication administration and dosages are less likely to use or overuse medications as compared to patients whose medication is regulated by a physician or nurse [18]. It is well established that patients offered a collaborative role in decision-making are more likely to conform to medical recommendations and treatment regimens [16].

Successful evaluation of therapeutic outcomes is partially contingent on the assessment of adherence; treatment compliance is critical to understanding several factors including the efficacy and safety of prescription drugs. There are limited clinical studies focused on patient adherence in clinical drug trials, and few investigations have evaluated strategies for enhancing patient participation [19].

The FDA has set forth clear and explicit guidelines by which clinical pharmaceutical trials are expect to be conducted; it is presumed that the majority of clinical drug trials identify the issue of adherence when interpreting the results [20]. However, adherence is quite possibly a variable that is overlooked. The overall purpose of this present study is to determine whether clinical trials involving psychiatric drugs (e.g., antidepressants, anxiolytics, antipsychotics…) are, in fact, controlling and/or measuring adherence in their procedures and whether researchers are reporting adherence in subsequent publications.

Since the issue of medication adherence is so widespread and a problem variable in research, it is not surprising that the U.S. Department of Health and Human Services offers grants towards program development to improve medication adherence. Currently, the U.S. DHH has funds allocated towards research into improving adherence in several patient populations (e.g., adolescents) [21]. The information is welcomed and should provide some answers as to developing a multimodal and effective method of increasing patient compliance.

Rationale

Based partially on the Gottlieb et al. study and the current literature, it is our assumption that if authors of published clinical trial studies, in peer-reviewed journals, attempted to control for adherence

or compliance, the word itself (adherence or compliance) would be mentioned somewhere in the anatomy of the publications. A brief manual review of some of the articles queried showed that not all articles which contained the word adherence, as an example, actually measured for treatment adherence. Rather, the word was used anecdotally in reference to past studies or issues with adherence, not in an attempt to measure or control for it. This is important to keep in mind and should be considered as in future studies of this nature.

For this study, a review of clinical drug studies published over the last 10 years was conducted by automated searches via electronic databases, selecting some of the most widely used databases at research universities and across clinical settings. Searches were narrowed to publications focused on the following drug categories: antipsychotics, antidepressants, anticonvulsants, anxiolytics, stimulants, opioids, and mood stabilizers. These medications are common and widespread in both clinical drug trials and psychiatric practice.

In clinical drug studies, when measurement of adherence is unaccounted for, the interpretation of results and evaluation of drugs' efficacy may be compromised [22]. This is a review of the need for consistent control or measurement of medication adherence in clinical drug trials.

Methods

Procedures

This study incorporated the use of electronic database searches to locate specific keywords found in all fields containing articles and books. As an example, if any of the words typed into the key word phrase were located anywhere in the anatomy of the article or book (e.g., abstract, methods, results, discussion, etc.), that title was included in the results yielded and analyzed. For each of the four database studied, specific limiters were included while key word phrases were matched and exactly the same across all database searches.

Databases selected

We selected four major databases for this study. The databases are listed as: (1) Pub Med / Medline, (2) Science Direct, (3) Scirus, and (4) Scopus. These are some of the most commonly used databases and electronic search engines among college students and researchers in the health sciences. Students in the health and behavioral sciences utilize libraries and e-databases with which they are familiar. Tenopir and Read surveyed college students and doctoral researchers and found that 75% of undergraduates, 90.5% of master level students, and 83.3% of doctoral students used databases upon which they were specifically trained [23]. According to one study, Medline boasts a sensitivity rate of 72% and a specificity rate of 75% with regard to hit rates on articles in narrowly focused domains of research [24]. Gottlieb and colleagues showed that when compared to EMBASE, BIOSIS, LILACS, Medline yielded 20% of non-replicated studies when reviewers searched the "prevalence of maternal mortality and morbidity from 1997 to 2002" [1]. Since this present study involves the use of specific keyword phrases in popular electronic databases, such statistics are useful in justifying the strengths of certain e-databases over others. In health science related academic studies, authors suggest that pilot database searches begin with Medline and then extend into other databases [25]. Interestingly, the results of the present study showed PubMed, which accesses Medline, to have the lowest hit rates of clinical drug trial articles containing the words adherence or compliance.

Authors set the final search parameters for the automated search and limited the electronic database search to peer-reviewed, journal articles and books related to clinical drug trials, conducted between 2002 and 2012. Although very few differences exist between databases in terms of limiter / parameter settings, mild differences in parameter settings and online templates require that each database be reviewed independently and that the reader is made aware of the slight variations in limiter settings found. Thusly, what follows shortly will include a review of the search query methods specific to each of the four databases.

Also, the electronic database searches were limited to the following drug classes: (1) antidepressants, (2) antipsychotics, (3) anticonvulsants, (4) anxiolytics, (5) stimulants, (6) opioids, and (7) mood stabilizers. These particular drugs represent the largest classes of drugs studied in clinical-trials (G. Gottlieb, personal communication, August, 2011). They are some of the most popular and most commonly prescribed categories of drugs (Los Angeles County Department of Mental Health [LCDMH], 2012). Keywords remained uniform and consistent across automated searches on all four drug class categories. Authors are not extrapolating the results to all drug trials.

Since the literature shows that both the term adherence and the term compliance are used interchangeably, this study also examined the hit rates between searches involving *adherence* versus *compliance* (Tables 1-4).

Keyword searches and limiters for Pubmed

Before keyword phrases can be imputed for direct query into publications, limiters are set to narrow the search. For this study, we queried PubMed under two conditions: one in which the limiter setting on PubMed for "clinical trial" was depressed and one in which it was not. In both cases, the keyword phrases involved still included the actual words clinical drug trials. The results were not significantly different based on whether the PubMed setting of clinical trial was depressed or not, but it is probably worth noting. Additional limiters used for the PubMed searches included human subjects, all fields, last 10 years, access to full text and all publication types.

Once limiters were set, the search queries involved the following phrases:

- Clinical drug trials AND antidepressants
- Clinical drug trials AND antidepressants AND adherence
- Clinical drug trials AND antidepressants AND compliance
- Clinical drug trials AND antipsychotics
- Clinical drug trials AND antipsychotics AND adherence
- Clinical drug trials AND antipsychotics AND compliance
- Clinical drug trials AND anticonvulsants
- Clinical drug trials AND anticonvulsants AND adherence
- Clinical drug trials AND anticonvulsants AND compliance
- Clinical drug trials AND anxiolytics
- Clinical drug trials AND anxiolytics AND adherence
- Clinical drug trials AND anxiolytics AND compliance
- Clinical drug trials AND stimulants
- Clinical drug trials AND stimulants AND adherence
- Clinical drug trials AND stimulants AND compliance
- Clinical drug trials AND opioids
- Clinical drug trials AND opioids AND adherence
- Clinical drug trials AND opioids AND compliance
- Clinical drug trials AND mood stabilizers
- Clinical drug trials AND mood stabilizers AND adherence
- Clinical drug trials AND mood stabilizers AND compliance

The same search strings were used across all seven drug categories.

It is interesting to note that changing the order of the words in the search phrase did not change the number of articles yielded.

Keyword searches and limiters for Science Direct

Limiters used for the Science Direct searches included human subjects, all fields, last 10 years, access to full text and all publication types. Search phrases used paralleled the search phrases listed under the PubMed queries.

Keyword searches and limiters for Scirus

Limiters used for the SCIRUS searches included human subjects, all fields, last 10 years, access to full text and all publication types. Search phrases used paralleled the search phrases listed under the PubMed queries.

Keyword searches and limiters for Scopus

Limiters used for the SCOPUS searches included human subjects, all fields, last 10 years, access to full text and all publication types. Search phrases used paralleled the search phrases listed under the PubMed queries.

Design

Basic distribution of frequencies, percentages and proportions are examined. Categorical variables analyzed include the four databases searched (PubMed, Science Direct, Scirus, and Scopus), drug classes, and hit rates based on search phrase type (adherence v. compliance). There are several levels of analyses. The first will involve a description of the observed frequencies and percentages of hit rates and a summative review of one of the populations of interest: electronic journal database. A second analysis will examine any significant differences between using the word "adherence" and using the word "compliance" in search phrases in terms of the outcome variable of proportions of articles. A third analysis will focus on identifying any statistical differences between drug classes for searches involving the word "compliance". We chose to narrow the final search to results containing the world compliance because compliance had the larger percentage rates overall.

In summary, a review of literature published in the last 10 years was undertaken to identify:

(1) The extent to which drug trial research studies considered and/or attempted to control for patient adherence to their prescribed medication regimens.

(2) The difference between search phrases and results yielded based on whether the term adherence or the term compliance was used.

(3) Any differences between drug classes on proportions of articles retrieved when compliance was used in search phrases.

Materials

Databases were accessed through the Pepperdine University remote library and electronic journal database system. Data was analyzed through IBM SPSS Advanced Statistics (version 19). The list of the specific portals for each database follows the appendices.

Statistical Procedures

An analysis of descriptive statistics including frequencies and proportions were conducted with SPSS (version 19). An examination of any statistical significance between hit rates based on "adherence" or "compliance" search phrases was conducted via a Chi square test of independence. Four additional Chi square tests of independence were conducted with the variables Type of Drug and Whether or Not Compliance was checked.

Results

Preliminary analysis

The preliminary analysis provides a description of population characteristics (databases searched) and percentages for hit rates based on adherence versus compliance search phrases.

Although past studies show Medline to yield higher hit rates for narrowly focused domains of research, our study showed that PubMed, which accesses Medline, yielded the lowest hit rates of clinical drug trial publications containing the words adherence or compliance when compared to the hit rates of Science Direct, Scirus, and Scopus.

The NCBI database, which houses PubMed and Medline, also covers a variety of other databases for the natural sciences such as Nucleotide, GEO profiles, Pub Chem Substance and others. The data for this analysis considered the hit rates for PubMed and Medline only. The analysis revealed that the majority of articles found under each drug class, when either the search phrase of adherence or compliance was used, neglected to control for or report attempts at measuring adherence / compliance. It is important to note that in the primary analysis of the PubMed database, the limiter setting for clinical trial was not depressed. However, in a second analysis of PubMed using the same phrases and drug classes, the clinical trial setting was used. The hit rates between the two settings did not result in marked differences of proportions yielded. To maintain conservation, an examination of the second setting in which the clinical trial box was checked showed that of the 15048 articles retrieved when the search phrase "clinical drug trials AND antidepressants" was used, only 155 (aprox 1%) of the articles mentioned adherence somewhere in the anatomy of the article. The same pattern emerged across all drug classes and regardless of whether adherence or compliance was used in the search phrase (Tables 1 through 4). The following table shows the hit rates, percentages of hit rates based on search phrase type (adherence versus compliance), and drug classes for PubMed / Medline. The results of the remaining three databases follow similar trends. Science Direct Results are found in Table 2; Scirus results in Table 3, and; Scopus results in Table 4 at the conclusion of this paper.

Adherence vs. compliance

Each combination of database and drug (e.g. Science Direct/ Antidepressants) was examined separately to compare searches using the word "adherence" with searches using the word "compliance" on the percentage of articles that included a check for adherence or compliance. To test whether there was a difference between the percentage (proportion) of articles checking adherence and the percentage (proportion) checking compliance, a Chi square test of independence was run for each type of drug in each database. This procedure is equivalent to comparing the percentage (proportion) for adherence to the percentage (proportion) for compliance [26]. Because of the large number of statistical tests conducted, applying Bonferroni's adjustment procedure, an alpha level of.05/32=.0016 should be used to interpret the results.

For the Science Direct database, all tests showed a significant difference between the percentage checking adherence and the percentage checking compliance, with a higher percentage checking compliance than adherence (Table 2). For the Scirus database, the

results were the same (Table 3). For the Scopus database, all differences were significant, except for Anxiolytics (Table 4). And for the NCBI database, all differences were significant, except for Stimulants and Mood stabilizers. In all cases where there was a significant difference between percentages, the percentage of studies checking compliance was higher than the percentage checking adherence.

Differences among types of drugs

For each database, the percentage of articles reporting that there was a check for compliance was compared across the seven types of drugs. Thus, four Chi square tests of independence were conducted with the variables Type of Drug and Whether or Not Compliance was checked. This procedure is equivalent to comparing the percentages (proportions) of articles that checked for compliance across the different types of drugs to determine whether they differ. All tests were significant at p <.001, demonstrating that the types of drugs did differ in the percentage of articles on the drug that checked for compliance.

For the Science Direct database, compliance was most often checked for Mood stabilizers (29.0%) and least often for Stimulants (18.5%; Tables 2 & 5). For the Scirus database, compliance was most often checked for Anticonvulsants (32.7%) and least often for Antidepressants (15.4%; Tables 3 & 6). For the Scopus database, compliance was most often checked for Antipsychotics (16.8%) and least often for Anticonvulsants (6.9%; Tables 4 & 7). And for the NCBI database, compliance was most often checked for Antipsychotics (3.0%) and least often for Anxiolytics (0.9%; Tables 1 & 8). (Mood stabilizers had to be eliminated from this last analysis because of an expected frequency less than 5).

Discussion

The results of this study support the hypothesis; a majority of clinical drug trials assessing the efficacy of psychotropic drugs did not control for medication adherence. Results showed that when queries contained the word "compliance", hit rates were significantly higher as compared to the hit rates when the keyword "adherence" was used. This held true for all four databases that were utilized in the study. There were significant differences between drug categories in terms of the proportion of articles that mentioned the word "compliance". Depending on the database, percentage rates per drug classes varied. Compliance was most common for Antipsychotics (3.0%) and least often for Anxiolytics (0.9%; Table 1) in the NCBI database. Compliance was found most often for Mood stabilizers (29.0%) and least often for Stimulants (18.5%; Table 2) when Science Direct was searched. Compliance was found most often for Anticonvulsants (32.7%) and least often for Antidepressants (15.4%; Table 3) in the Scirus database, and compliance was most checked often for Antipsychotics (16.8%) and least often for Anticonvulsants (6.9%; Table 4) in Scopus. This point to the lack of equivalency in publications across a variety of psychiatric drug classes. As such, all the concerns previously discussed emerge as foci for discussion.

However, cautious interpretation is advised due to the limitations of this study, which are discussed at length later. Errors in database retrieval, search phrase issues and possible problems with parameter or limiter settings should be considered. Still, the statistics overwhelmingly support the hypothesis that a low frequency of clinical drug trial articles, published in peer reviewed journals and found via popular scientific databases, actually mention adherence and / or compliance. Thus, the issues surrounding the safety and efficacy of many types of psychiatric drugs, ranging from antidepressants to stimulants, are raised.

When examining the result globally, the range of articles in which "compliance" was mentioned across all four databases and drug categories was.9% (anxiolytics in PubMed/Medline) to 32.7% (anticonvulsants in Science Direct). At the conservative end, approximately 67.3% of clinical drug trials neglect or fail to mention compliance in their publications. In a more liberal estimate, that number increases to an astonishing 99%. When search was limited to articles about anxiolytics, and accessed through PubMed, 99% of articles lacked mention of the term "compliance".

Medication Side Effects Profiles and Patient Compliance

In examining the seven drug categories chosen for this study, one is overwhelmed by the plethora of pharmaceuticals and synthetic drugs available in each class. Each class of drugs present side effect profiles that coalesce, bleed into and overlap with the side effect profiles of others drugs. Often in clinical practice, physicians will treat patients

NCBI Database Includes PubMed / Medline	***Antidepressants***		***Antipsychotics***		***Anticonvulsants***		***Anxiolytics***		***Stimulants***		***Opioids***		***Mood stabilizers***	
Search Phrase Limiters used: human + all fields + last ten years +access to full text	Clinical drug trials + antidepressants		Clinical drug trials + antipsychotics		Clinical drug trials + anticonvulsants		Clinical drug trials + anxiolytics		Clinical drug trials + stimulants		Clinical drug trials + opioids		Clinical drug trials + mood stabilizers	
Total articles found in search (pub med section only)	15048		12766		13923		10922		1375		6192		250 + 51 + 4	
Search Phrase Limiters used: human + all fields + last ten years +access to full text	Adherence **or** compliance + Clinical drug trials + antidepressants		Adherence **or** compliance + Clinical drug trials + antipsychotics		Adherence **or** compliance + Clinical drug trials + anticonvulsants		Adherence **or** compliance + Clinical drug trials + anxiolytics		Adherence **or** compliance + Clinical drug trials + stimulants		Adherence **or** compliance + Clinical drug trials + opioids		Adherence **or** compliance + Clinical drug trials + mood stabilizers	
Total articles found in search	**Adhr**	**Comp**	**Adhr**	**Comp**	**Adhr**	**Comp**	**Adhr**	**Comp**	**Adhr**	**Comp**	**Adhr**	**Comp**	**Adhr**	**Comp**
	155	**332**	**187**	**388**	**51**	**171**	**13**	**93**	**14**	**35**	**63**	**156**	**1**	**7**
Percentage of total articles in this topic in pub med alone:	**1.0%**	**2.2%**	**1.5%**	**3.0%**	**.4%**	**1.2%**	**.1**	**.9%**	**1.0%**	**2.5%**	**1.0%**	**2.5%**	**.4%**	**2.8%**

Note: All differences were significant at p <.001, except for Stimulants, which was significant at p <.005, and Mood stabilizers, which was not significant

Table 1: Comparison of Percentages of Articles Testing Adherence (Adher) vs. Compliance (Compli) for NCBI Database.

Science Direct	*Antidepressants*		*Antipsychotics*		*Anti-convulsants*		*Anxiolytics*		*Stimulants*		*Opioids*		*Mood stabilizers*	
Search Phrase **Limiters used:** human + all fields + last ten years +access to full text	Clinical drug trials + antidepressants		Clinical drug trials + antipsychotics		Clinical drug trials + anticonvulsants		Clinical drug trials + anxiolytics		Clinical drug trials + stimulants		Clinical drug trials + opioids		Clinical drug trials + mood stabilizers	
Total articles found in search	37219		12444		17031		4563		17322		15400		4155	
Search Phrase **Limiters used:** all fields + all document types + last ten years +access to full text Includes life sciences, health sciences, physical sciences, social sciences and humanities	Adherence **or** compliance+ Clinical drug trials + antidepressants		Adherence **or** compliance + Clinical drug trials + antipsychotics		Adherence **or** compliance + Clinical drug trials + anticonvulsants		Adherence **or** compliance + Clinical drug trials + anxiolytics		Adherence **or** compliance + Clinical drug trials + stimulants		Adherence **or** compliance + Clinical drug trials + opioids		Adherence **or** compliance + Clinical drug trials + mood stabilizers	
Total articles found in search **Percentage of total articles in this topic:**	**Adhr** **4509** **12.1%**	**Comp** **7980** **21.4%**	**Adhr** **1880** **15.1%**	**Comp** **3206** **25.8%**	**Adhr** **1533** **9.0%**	**Comp** **3292** **19.3%**	**Adhr** **496** **10.9%**	**Comp** **984** **21.6%**	**Adhr** **1826** **10.5%**	**Comp** **3281** **18.9%**	**Adhr** **1544** **10.0%**	**Comp** **3016** **19.6%**	**Adhr** **1** **.4%**	**Comp** **7** **2.8%**

Note: All differences were significant at p < .001

Table 2: Comparison of Percentages of Articles Testing Adherence (Adhr) vs. Compliance (Comp) for Science Direct Database.

Scirus	*Antidepressants*		*Antipsychotics*		*Anti-convulsants*		*Anxiolytics*		*Stimulants*		*Opioids*		*Mood stabilizers*	
Search Phrase **Limiters used:** human + all fields + last ten years +access to full text	Clinical drug trials + antidepressants		Clinical drug trials + antipsychotics		Clinical drug trials + anticonvulsants		Clinical drug trials + anxiolytics		Clinical drug trials + stimulants		Clinical drug trials + opioids		Clinical drug trials + mood Stbz	
Total articles found in search	119,528		37046		20050		9217		30449		43454		9002	
Search Phrase **Limiters used: all fields + all document types + last ten years +access to full text**	Adherence **or** compliance + Clinical drug trials + antidepressants		Adherence **or** compliance + Clinical drug trials + antipsychotics		Adherence **or** compliance + Clinical drug trials + anticonvulsants		Adherence **or** compliance + Clinical drug trials + anxiolytics		Adherence **or** compliance + Clinical drug trials + stimulants		Adherence **or** compliance + Clinical drug trials + opioids		Adherence **or** compliance + Clinical drug trials + mood stabilizers	
Total articles found in search **Percentage of total articles in this topic:**	**Adhr** **14477** **12.1%**	**Comp** **18413** **15.4%**	**Adhr** **1880** **15.1%**	**Comp** **8819** **23.8**	**Adhr** **3620** **18.1%**	**Comp** **6564** **32.7%**	**Adhr** **1657** **18.0%**	**Comp** **2817** **30.6%**	**Adhr** **6895** **22.6%**	**Comp** **7514** **24.7%**	**Adhr** **6354** **14.6%**	**Comp** **8903** **20.5%**	**Adhr** **2333** **25.9%**	**Comp** **2786** **30.9%**

Note: All differences were significant at p < .001

Table 3: Comparison of Percentages of Articles Testing Adherence (Adhr) vs. Compliance (Comp) for Scirus Database.

with a cocktail of drugs, providing another layer of questions as to drug interaction and side effect interactions. In fact, many clinics and mental health counseling centers are turning towards evidence-based treatments, with psychotropic medications used as the frontline approach to treatment of persistent and pervasive mental illnesses (LCDMH, 2012).

A patient diagnosed with bipolar disorder may receive a cocktail consisting of an antidepressant (usually SSRI's for BD), a mood stabilizer and in some cases, an antipsychotic. The side effects profile for antipsychotics can encompass a wide range of distressing phenomena such as extrapyramidal effects (e.g., dystonia, tardive dyskinesia, etc.), metabolic syndrome, gastrointestinal problems, hyperprolactinemia, sedation and others. To treat the side effects, a physician may then prescribe, for example when treating dystonia or dyskinesia, an anticholinergic like benzotropine mesylate or an anxiolytic (B. Moore, personal communication, March, 2012). Some of the effects of older antipsychotics include nearly permanent neurological changes. These changes include disruptions in dopaminergic and serotonergic production mechanisms that affect both the frontal and mesolimbic regions of the brain. These neuronal pathways are

Scopus	*Anti-depressants*		*Antipsychotics*		*Anticonvulsants*		*Anxiolytics*		*Stimulants*		*Opioids*		*Mood stabilizers*	
Search Phrase **Limiters used:** human + all fields + last ten years +access to full text	Clinical drug trials + antidepressants		Clinical drug trials + antipsychotics		Clinical drug trials + anticonvulsants		Clinical drug trials + anxiolytics		Clinical drug trials + stimulants		Clinical drug trials + opioids		Clinical drug trials + mood Stbz	
Total articles found in search	40659		13728		13926		1386		10047		11275		4871	
Search Phrase **Limiters used: all fields + all document types + last ten years +access to full text Includes life sciences, health sciences, physical sciences, social sciences and humanities**	Adherence **or** compliance + Clinical drug trials + antidepressants		Adherence **or** compliance + Clinical drug trials + antipsychotics		Adherence **or** compliance + Clinical drug trials + anticonvulsants		Adherence **or** compliance + Clinical drug trials + anxiolytics		Adherence **or** compliance + Clinical drug trials + stimulants		Adherence **or** compliance + Clinical drug trials + opioids		Adherence **or** compliance + Clinical drug trials + mood Stbz	
Total articles found in search	**Adhr** **3821**	**Comp** **4650**	**Adhr** **1599**	**Comp** **2304**	**Adhr** **503**	**Comp** **960**	**Adhr** **83**	**Comp** **121**	**Adhr** **653**	**Comp** **984**	**Adhr** **491**	**Comp** **846**	**Adhr** **589**	**Comp** **722**
Percentage of total articles in this topic:	**9.4%**	**11.4%**	**11.6%**	**16.8%**	**3.6%**	**6.9%**	**6.0%**	**8.7%**	**6.5%**	**9.8%**	**4.4%**	**7.5%**	**12.1%**	**14.8%**

Note: All differences were significant at $p < .001$, except for Anxiolytics, which was significant at $p < .01$

Table 4: Comparison of Percentages of Articles Testing Adherence (Adhr) vs.Compliance (Comp) for Scopus Database .

			Compliance		Total
			Checked	Not Checked	
Drug	Antidepressants	Count	332	14716	15048
		% within Drug	2.2%	97.8%	100.0%
	Antipsychotics	Count	388	12378	12766
		% within Drug	3.0%	97.0%	100.0%
	Anticonvulsants	Count	171	13752	13923
		% within Drug	1.2%	98.8%	100.0%
	Anxiolytics	Count	93	10829	10922
		% within Drug	.9%	99.1%	100.0%
	Stimulants	Count	35	1340	1375
		% within Drug	2.5%	97.5%	100.0%
	Opiods	Count	156	6036	6192
		% within Drug	2.5%	97.5%	100.0%
Total		Count	1175	59051	60226
		% within Drug	2.0%	98.0%	100.0%

Drug * Compliance Crosstabulation

Table 5: NCBI Database.

			Compliance		Total
			Checked	Not Checked	
Drug	Antidepressants	Count	7980	29239	37219
		% within Drug	21.4%	78.6%	100.0%
	Antipsychotics	Count	3202	9238	12440
		% within Drug	25.7%	74.3%	100.0%
	Anticonvulsants	Count	3292	13739	17031
		% within Drug	19.3%	80.7%	100.0%
	Anxiolytics	Count	984	3579	4563
		% within Drug	21.6%	78.4%	100.0%
	Stimulants	Count	3181	14041	17222
		% within Drug	18.5%	81.5%	100.0%
	Opioids	Count	3016	12384	15400
		% within Drug	19.6%	80.4%	100.0%
	Mood stabilizers	Count	1204	2951	4155
		% within Drug	29.0%	71.0%	100.0%
Total		Count	22859	85171	108030
		% within Drug	21.2%	78.8%	100.0%

Drug * Compliance Crosstabulation

Table 6: Science Direct Database.

intrinsic to stable dopaminergic and serotonergic function. Brain centers like the susbtantia nigra that are involved in movement disorders may be impacted in long-term users of certain antipsychotics creating a Parkinsonian syndrome (LACDMH, 2012). Changes to the hypothalamic pituitary axis can impact thyroid function, reproduction, and metabolism – to name a few of the long-term consequences.

Certainly, it is quite understandable, at least from a humanistic paradigm, the tiring and deleterious effects of such drug regimens. In some cases, the ensuing side effects and drug interactions seem too high a cost to pay for symptom relief. Rather, it is completely understandable and perhaps expected that people would avoid such physiological changes if the theory that patients attend to a "feel good" rule ~ applies. The ultimate problem, therefore, is not in understanding why lack of

			Compliance		Total
			Checked	Not Checked	
Drug	Antidepressants	Count	18413	101115	119528
		% within Drug	15.4%	84.6%	100.0%
	Antipsychotics	Count	8819	28227	37046
		% within Drug	23.8%	76.2%	100.0%
	Anticonvulsants	Count	6564	13486	20050
		% within Drug	32.7%	67.3%	100.0%
	Anxiolytics	Count	2817	6400	9217
		% within Drug	30.6%	69.4%	100.0%
	Stimulants	Count	7514	22935	30449
		% within Drug	24.7%	75.3%	100.0%
	Opioids	Count	8903	34551	43454
		% within Drug	20.5%	79.5%	100.0%
	Mood stabilizers	Count	2786	6216	9002
		% within Drug	30.9%	69.1%	100.0%
Total		Count	55816	212930	268746
		% within Drug	20.8%	79.2%	100.0%

Drug * Compliance Crosstabulation

Table 7: Scirus Database.

			Compliance		Total
			Checked	Not Checked	
Drug	Antidepressants	Count	4650	36009	40659
		% within Drug	11.4%	88.6%	100.0%
	Antipsychotics	Count	2304	11424	13728
		% within Drug	16.8%	83.2%	100.0%
	Anticonvulsants	Count	960	12966	13926
		% within Drug	6.9%	93.1%	100.0%
	Anxiolytics	Count	121	1265	1386
		% within Drug	8.7%	91.3%	100.0%
	Stimulants	Count	984	9063	10047
		% within Drug	9.8%	90.2%	100.0%
	Opioids	Count	846	10429	11275
		% within Drug	7.5%	92.5%	100.0%
	Mood stabilizers	Count	722	4149	4871
		% within Drug	14.8%	85.2%	100.0%
Total		Count	10587	85305	95892
		% within Drug	11.0%	89.0%	100.0%

Drug * Compliance Crosstabulation

Table 8: Scopus Database.

adherence is so commonplace, but rather what can be done to improve medication adherence and compliance.

Measuring adherence

In the Gottlieb et al. study, authors examined several ways in which adherence is measured in both clinical and scientific settings. In the studies that addressed medication adherence, methods of assessment often lacked rigor. Common measurements for adherence include self-report, clinical judgment, pill-count data, and pharmacy records. A drawback to these methods is the indirect nature of such measurements. Ingestion of medications and adequate dosage is not easily accounted for. Scientists utilize physiological measurements such as urine toxicology screening and blood assays in more current studies (D. Turk, personal communication, March, 2011). Electronic monitoring (EM) is considered optimal in accuracy and cost efficacy [15]. EM is time stamped, which allows confirmation of when patients: opened bottles, dispensed drugs or activated a canister. Unfortunately, "…EM does not permit confirmation that the patient actually consumed medication that was removed" (D. Turk, Personal Communication, March, 2011) [1]. Positive attributes of EM include increased sensitivity to detecting drug non-adherence when compared to other methods [19,26]. EM also supplies information about medication taking patterns and patterns of non-compliant behavior (e.g., missing evening doses). According to past studies on EM, omissions of doses rather than additional or modified doses, or delays in timing of doses, modulate disruptions in medication adherence [26].

Limitations

There are several limitations to this study. The first is the possibility of measurement error in the automated searches. The search phrases used for this study may not have identified articles that actually controlled for adherence, using words not specified by our search queries. This is a problem in trying to be exhaustive for such large sets of studies. Search phrases or key words may not have been all inclusive and lack of sensitivity in the automated searches may be a contributing factor.

Automated searches relied on the assumption that if a researcher included a measure of adherence in their study design, there would be specific mention of adherence and/or compliance in the title, abstract, body, or methods section of the published article. It is possible that a past researcher may have included a measure of adherence or compliance in such a way that the search engine failed to identify the "adherence" or "compliance" key terms.

Another limitation is the fact that we only searched four electronic databases: PubMed / Medline, Science Direct, Scirus and Scopus. In our defense, these are very popular databases among college and post-doctoral researchers, but our results may not generalize to all electronic databases or search engines. Further, only seven drug categories were examined. Database searches of specific medications under each drug class (e.g., fluoexetine, citalopram, olanzapine, dextroamphetamine) were not conducted. However, such a search would require perspicuity and endurance in identifying and organizing brand versus generic pharmaceuticals; inspiration for another study.

A final limitation is evidenced by the fact that we only examined the findings from automated searches. Unlike the Gottlieb et al. study, which we were attempting to improve upon and replicate, a manual search was not included in the present design. This is something that should be considered in future studies that attempt to confirm present findings. These limitations, rather than being viewed as dyslogistic of our efforts, are better viewed as fuel for future research.

Readers are also reminded that the FDA and other regulatory agencies power their own private websites, some of which contain exhaustive databases. The results of this study may not generalize to all databases, and in some cases, underestimate the number of articles in which the variable of adherence was controlled and measured.

Conclusion

The evidence suggests that medication adherence in medical research is not a formally assessed variable; neither is it mentioned in the majority of publications available through popular electronic

and scientific databases. The implications of such a gap in clinical trial research are disconcerting and call into question the uniformity, consistency, and safety of prescription medications. Clinical drug research may be compromised given that the precise level of drug intake during the research study period may be unknown. Conclusions about drug efficacy, safety, application and long-term effects may have questionable validity without proper assurance of adherence or compliance during the research.

This study sheds more light on a variable which has received inadequate attention in clinical drug trials, and the present findings complement and support the findings by Gottlieb and others. Two factors assure that conclusions about drug safety or efficacy are valid: 1) the medication should affect a disease or symptoms beyond what would be demonstrated by a placebo and 2) the patient must consume the medication in a prescribed dosage. Evaluations of drug efficacy and safety ride upon the assumption that all drug research adhere to strict protocols and provisions for measuring adherence or compliance. Stronger efforts to monitor medication adherence should enhance conclusions posited regarding the clinical efficacy of the drug under investigation.

List of Databases

1. The National Center for Biotechnology Information advances science and health by providing access to biomedical and genomic information. http://www.ncbi.nlm.nih.gov.lib.pepperdine.edu/
2. Science Direct:

http://www.sciencedirect.com.lib.pepperdine.edu/science?_ob=MiamiSearchURL&_method=requestForm&_btn=Y&_acct=C000024718&_version=1&_urlVersion=1&_userid=501803&md5=73fca5ac80409800572088a20073d814

3. Scirus

http://www.scirus.com.lib.pepperdine.edu/srsapp/advanced/index.jsp?q1=

4. Scopus

http://www.scirus.com.lib.pepperdine.edu/srsapp/advanced/index.jsp?q1=

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