A Systematic Literature Review of Behavioral Risk Factors Associated with Initial Medication Adherence

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Abstract

**Background:** Numerous factors pertaining to poor medication adherence in chronically ill patients are well documented, but the paucity of studies concerning early treatment course experiences represents a significant knowledge gap. Interventions targeting this crucial initial phase can influence long-term adherence and outcomes. An international panel conducted a systematic literature review documenting behavioral risk factors related to initial adherence.

**Methods:** A comprehensive search of Pubmed, PsychInfo, and Web of Science covered published articles from 1966-2011. Independent reviewers abstracted eligible studies through a validated quality instrument, documenting methodological details and factors associated with adherence problems. Articles addressing numerous behavioral factors were deemed relevant if presenting primary data and quantitative findings following initial prescriptions.

**Results:** Our search identified 865 potentially relevant publications; upon full review, 24 met eligibility criteria. The mean Nichols quality assessment score was 47.2 (range 19-74), with excellent concordance between independent reviewers ($r=0.966$, $p<0.001$). Prevalent terminology defining early pharmacotherapy was first-fill, initial or primary adherence. A variety of methodological definitions and challenges synthesizing the findings were observed. Articles described the following risk factors commonly associated with initial adherence: patient characteristics (n=16), medication class (n=12), physical comorbidities (n=12), pharmacy copayments or out of pocket costs (n=11), health beliefs and provider communication (n=5), and a variety of other issues. Few studies reported specific health system factors, such as pharmacy location/information, prescribing provider licensure, or other non-patient dynamics.
Conclusion: Despite the implications for chronic medication adherence and clinical outcomes, a relatively small set of articles directly examined issues associated with initial adherence. Notwithstanding this lack of information, many observed risk factors are amenable to potential interventions, establishing a solid foundation for appropriate ongoing behaviors. Future research should continue investigating questions pertaining to initial prescriptions, emerging treatment barriers, and organizational efforts to promote better long-term adherence.

key words: systematic review, primary / initial medication adherence, behavioral risk factors, others?
Introduction

Medication adherence is defined as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regime” [1]. There are two types of medication adherence: initial adherence, where the patient fills the medication the first time it is prescribed and continued adherence, where the patient continues to refill the medication. Numerous factors pertaining to poor medication adherence in chronically ill patients are well documented. However, there exists a paucity of studies concerning experiences during the early treatment course (often referred to as either “primary, initial, or first fill adherence”), representing a crucial knowledge gap. Accurately determining the rate of initial adherence is a challenge, because there is currently no validated, systematic means of determining this through existing records. However, in a national study comprising the vast majority of retail pharmacy prescriptions in the U.S., the prevalence of new fill abandonment was 6.3% in 2009, up from 5.1% the prior year [2]. The problem with the measurement of initial adherence stems from an inability to connect the actions that occur in the physician’s office with the patient’s actions outside the physician’s office. In a survey of more than 9,000 patients, the Boston Consulting Group (BCG) reported that 18% of patients did not fill a prescription in the past 12 months, with 10% giving as a primary reason for nonadherence that they “can’t get prescription filled, picked up or delivered” [3]. Other small, non-generalizable studies about the rate of initial adherence do exist, but are insufficient to establish a true estimate of the rate of initial non-adherence. These studies have only either only studied specific conditions such as asthma [4] or in specific settings such as pharmacies [5].
Furthermore, starting a medication regimen (i.e., initial adherence) is the beginning of a complex series of behavior changes that can have a long term effect on a patient’s health and well-being. If the patient never starts a chronic medication, then there is no need to worry about refilling it. Understanding the factors that influence this initial behavior can lead the clinician to identify targeted interventions at this crucial stage in the treatment process to improve the patient’s adherence behaviors and longer term outcomes. To that end, the Medication Adherence and Persistence (MAP) working group of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) undertook this systematic review of the literature to identify the current state of the research in this area. The intent of this analysis is to summarize the current body of literature focused upon initial medication adherence, identify the research strengths and gaps, document potential behavioral or psychosocial risk factors associated with poor adherence during this early treatment phase, and offer recommendations for further research in this area.

Methods

An international panel of researchers with considerable expertise in the topic area conducted a comprehensive, systematic review of the published literature documenting risk factors related to initial adherence across multiple chronic health conditions. This literature search of multiple databases covered the period from 1966 through August 2011, including Medline (PubMed, Ovid), the Cochrane library, PsycInfo, Scopus, Web of Science, Embase and CINAHL. The following standardized search terms were used for our central objective: primary, initial and early (non)adherence, primary, initial and early (non) compliance, and first fill adherence / compliance. These key terms were cross referenced with the following behavioral or
psychosocial factors: medication beliefs / trust (regarding its benefits), illness insight (perspective that health condition is serious and/or warrants treatment), therapeutic alliance / provider relationship, patient centered care, self-activation, internal locus of control, stigma, side effects, language preference / health literacy, acculturation / cultural preference, socioeconomic status, social support, homelessness, cognitive limitations, complementary or alternative medicine (CAM), access to care (e.g., distance, transportation, other problems), substance abuse, other comorbidities, treatment regimen complexity, and medication cost, copayments / pharmacy benefits. We also iteratively searched the bibliographies of included articles as well as relevant review papers for additional eligible publications.

Limiting the selection to publications in English, we required that the published studies describe work conducted on primary data analysis only, with additional exclusions made for case series with fewer than 10 patients, or articles presenting only conceptual or theoretical work. In an effort to restrict the focus of our study upon a limited definition of primary or initial adherence, further discussions and a complete review of articles led to excluding those that dealt with adherence during the early treatment course or longitudinal persistence, rather than the very first prescription and factors associated with adherence problems of initial fills.

Two independent reviewers first assessed all eligible articles through a validated quality instrument documenting methodological details; the Nichols tool evaluates multiple dimensions of research quality, including study design, how disease conditions were defined, and descriptions of adherence measurement [6]. Scaled scores are assigned to a range from 0-100, and we report the mean and variance for all included articles. Each article was then fully extracted by sets of at least two independent reviewers to document information concerning.
adherence definitions (e.g., primary, initial, other), study type (RCT, observational, prospective),
the pharmacy data collection method (ordered prescriptions versus filled claims, or patient self-
report), methodology concerning adherence measurement, (e.g., number of fills within 90 days,
medication possession ratio, other techniques), acute and/or chronic disease state and specific
diagnoses, and therapeutic drug class. Additional information was collected on patient
demographics (including race/culture, SES, health literacy), practitioner type (primary care,
specialist, nurse practitioner, etc.), prescribing system (electronic, paper), location of dispensing
pharmacy (HMO, chain, community), and patient insurance type and/or pharmacy copayments.
Finally, as the primary outcome of interest for this review, significant factors affecting initial
adherence as documented by the article authors were summarized, along with observations
concerning study limitations. After the comprehensive data extractions were completed and new
searches revealed no further included articles, the study team again reviewed and summarized
this data to confirm a final inclusion list, discuss terminology and central themes, and resolve
potential conflicts between reviewer pairs.

Results

Search Results:

Overall, the search of key terms identified 865 potentially relevant abstracts, of which
307 publication titles were deemed potentially eligible and the abstracts reviewed for additional
details. Of these, only 63 papers were determined to be likely relevant and therefore evaluated in
full by the entire study team to determine final inclusion. Based upon our definition of primary
or initial adherence which eliminated studies more broadly documenting early treatment
compliance, longitudinal persistence, or discontinuation over periods ranging from 1 month to
two years after the first prescription, only 24 articles made our final eligibility list. These
selected publications were then fully extracted and evaluated for quality per the aforementioned
description. Table 1 presents a summary of the final included articles. See Figure 1 for a flow
chart of the systematic search design. In terms of the assessed quality, the mean Nichols score for
these articles was 47.2 (sd 14.2) with a substantial range between 18.5 and 74.1. Both reviewers
closely agreed in their evaluations with an interclass correlation coefficient for the total score of
0.966 (95% CI 0.948 – 0.974, p<.01).

**Insert Table 1 and Figure 1 about here**

In terms of general observations concerning these studies, none were randomized trials and
few presented findings from prospective study designs; two were conducted from the prescriber
offices and their prescription data [7, 8] and four utilized prospective data collection by patient
survey [9-12]. Most articles, however, instead primarily relied upon observational or
retrospective examinations of secondary pharmacy datasets. Yet two studies also supplemented
their analyses with either telephone interviews [13] or a large number of survey responses [14] to
query patient reasons and other factors associated for primary non-compliance. Although about a
third of the analyses (8) examined medications for acute conditions, most covered patients with
one of several chronic health conditions over a wide range of physical and psychiatric disorders
or drug classes, including hypertension, diabetes, cardiovascular disease, depression or anxiety,
asthma, osteoporosis, epilepsy, cancer, and multiple sclerosis. Few articles provided much detail
concerning the specific prescriber (physician, nurse practitioner, other), information concerning the pharmacy prescription system used (e.g., electronic scripts, mail out fills), or whether the dispensing pharmacy service was part of the health system or a community pharmacy. In addition, no studies described provider, organizational or other non-patient factors potentially associated with initial adherence.

Study populations:

Cohort size varied greatly across the articles, ranging from small studies of 60 patients to extremely large populations of 5.2 million, covering a few hundred to over 10 million total prescriptions. In terms of demographic characteristics, the majority of participants in these studies were female (average 55%, range 32-62%), while the mean patient age in the 16 papers providing this data was 56.2 years (range 15 – 81+). Fourteen studies were conducted on predominantly Caucasian populations including three studies in Scandinavia, although the primary language spoken was not clarified; three of these studies provided a broad breakdown of multicultural populations. Eight publications did not report racial/ethnic demographics. The socioeconomic status of participants was not reported in 13 studies. However, six studies were conducted on individuals with higher incomes (for example, >$50,000 annual incomes and health insurance coverage. Five studies included predominantly lower socio-economic groups, whereas three studies reported smaller proportions of lower socio-economic groups. The specific type of health insurance was not stated in seven papers. When documented, health insurance benefits primarily consisted of pharmacy co-payment systems decreasing with total expenditures.
Two studies included fully insured participants while other articles described combinations of health insurance systems specific to the country of origin. Health literacy was not directly examined in 18 studies, although 6 studies reported some evidence of educational levels; one study reported 25% with some college [15], though the others note approximately 20% without a high school diploma.

Medication Adherence: Frequently Used Terminology and Methodology

As noted above, key terms used in the literature search consisted of the following four adjectives: 1) primary; 2) first; 3) initial; and 4) early, along with these five compliance terms: 1) adherence; 2) abandonment; 3) redemption; 4) persistence; and 5) discontinuation. With considerable overlap of definitions, the most prevalent adherence terminology was primary, used in 46% (11 of 24) of the eligible publications. Initial was the second most commonly used term, observed in 42% (10 of 24) of the eligible publications, followed by first-fill adherence which was found in 38% of the final articles. The term early adherence was only seen once in the eligible publications, along with a variety of other infrequently used terms including new or first prescription, treatment initiation, and index fill. Conducting an updated literature review on these additional terms did not reveal further eligible articles. Three studies best classified as prescription abandonment, defined as a patient not picking up a prescription that was filled at the pharmacy, were included in the final list as these articles also used another term for early adherence and appeared to loosely frame their studies in that context [15-17]. From the 63 articles thoroughly reviewed, 39 were excluded since although one of key search terms was used, it was clear that the studies did not examine the very first prescription. Instead, our review team
determined these articles presenting adherence findings over a period covering the early course of treatment, which ranged from about a month to over a year following the index prescription. As such, although these abstracts were picked up when using our search terminology (see Table xxx 2?), they were not appropriate for our more rigid definition of initial or first-fill adherence.

Adherence Measurement

As defined by the eligible study authors, the main outcome measure for determining rates of poor initial compliance was naturally the length of time from first prescription until it was filled by the patients, although this period varied and some alternatives approaches were observed. The most prevalent study period time frame was findings of a dichotomous fill (any versus none) within 30 days of the initial prescription [16, 18-23], although 2-3 months was also common [7, 8, 12, 14, 15, 17]; longer periods without a first prescription were also utilized several times, including 4-7 months [13, 24], and even up to a year [11, 25]. Survival analyses were also conducted twice, to examine length of time until a fill ranging from over the first 2 months [26] to 5 years [27]. However, although the terminology of primary adherence was utilized by several studies, suggesting a distinct first prescription, a broader perspective or use of multiple outcomes was noted in several publications. For example, the frequently employed medication possession ratio (MPR) greater than 80% over a 1-year period defined adherence persistence for Ko et al. [28], yet the authors also examined a 14-day prescription gap or delay following receipt of a coronary stent. Similarly, Kretzer et al. used a combination of MPR, gaps, or switches from an initial drug over a 12 month period [29]. In other studies, reasons for both initiating and discontinuing medications during a 6-month period were examined [9], as was the
percent of days covered (comparable to the MPR) for patients initiating treatment along with
prescription switches [30]. Finally, Wamala et al. documented the self-reported lack of fills
within 90 days of a prescription, yet it was unclear whether these were restricted to initial
treatment or any fills [10].

Prevalence of Poor Adherence

Based upon the aforementioned study definitions of adherence, we summarized the
reported rates of poor early compliance. Of the 20 articles with the clearest outcome definitions
(i.e., single outcome, no initial prescription within a finite number of months), the rates of
patients experiencing poor adherence varied between 2.3% and 50%. Recognizing the large
differential in sample sizes between 60 and over 5 million, the weighted average across
populations was 5.1% (sd 1.3%). When studies reported the total number prescriptions (n=6), the
poor adherence rates varied between 2% and 50%. A slightly more complex summary of
outcomes was observed in the four papers with longer observational windows or those looking at
multiple drug classes within a single study. For example, Ko et al. found prescription non-
initiation rates of 16% and 7% (one week and one year, respectively) following receipt of
coronary stents; longer term persistence of 16-26% at 3 to 6 months was calculated using the
MPR [28]. Krestzer and colleagues found poor compliance rates ranged between 25 – 55%
depending on drug class, as did Shrank et al. using the PDC measure over a year, finding rates of
21 – 65% across specific medication classes [30]. Results from the Wamala et al. study, not
distinguishing between initial versus any fill, found poor compliance rates between 4 – 11% by
drug class [10].
Behavioral Factors Associated with Poor Initial Adherence

Turning to the primary outcome of interest here, the authors also collectively examined numerous issues associated with initial adherence identified in these papers, arriving at a consensus of the most commonly reported psychosocial or behavioral risk factors. Table 3 presents a quantitative summary of the statistically significant findings from across the 24 published studies. The most prevalent factor addressed was, not surprisingly, demographics or other patient characteristics. A total of 16 articles presented the associated between primary adherence and several factors, notably age; although younger patients were often seen as substantially less compliant [11, 13, 16, 17, 22, 30], several articles observed that middle age or older patients experienced more difficulty with initial prescriptions [7, 10, 21, 23-25]. Low socioeconomic status was also frequently listed as an adherence barrier, primarily regarding income, but also individuals living alone or with poor social support [10, 16, 17, 19, 24, 28, 30], although Wroth & Pathman observed married patients were 30% more likely to have adherence problems [11]. Overall, men exhibited significantly better adherence in the few papers specifically reporting on gender [11, 16, 25, 30], but worse behavior in another study [13].

Race/ethnicity was less commonly examined, though minorities in general were less adherent [11, 19]; limited to initial antidepressant treatment, van Geffen also noted that non-Western immigrants failed to initiate treatment at higher rates [23]. Patients in rural areas were slightly less likely to fill first prescriptions in one study than considered geographic residency [16].

The next most frequently examined issue was observed adherence differences by drug class or specific medication (n=12). While actual rates are difficult to compare due to different
outcome measures, study populations, and selected drugs analyzed, a general summary suggests that patients more consistently failed to fill prescriptions for several medication types. Most notably, this included medications for dermatological conditions \([7, 25]\) and calcium channel blockers \([21, 26, 30]\), along with urinary tract or obstetrics medications and oral contraceptives \([7, 13, 30]\). Poor adherence rates were also high in individual studies for infections \([7]\), injectable anticoagulants \([24]\), loop diuretics \([21]\), antipsychotics \([16]\), and either nutritional supplements or cold and allergy medications \([16, 24]\). Conversely, better adherence rates were observed for ACE inhibitors \([21, 24, 30]\), statins \([24, 30]\), antibiotics \([13, 16]\), beta blockers \([21, 29]\), and opiates \([16]\). Beardon et al. and Ekedahl & Mansson frequently documented similar findings concerning both drugs with higher (cardiovascular, generally defined) and lower adherence rates (respiratory, musculoskeletal) \([7, 13]\). Other psychotropic drugs had mixed findings, with better adherence for anti-anxiety medications \([25]\), but antidepressants had better reported rates in one study \([16]\) while they were among the lowest in another comparative article \([24]\). Karter and colleagues compared three drug classes over a longer time period (i.e., outcomes of no fill, or only one fill during a 2-year window), finding that high cholesterol prescriptions were filled at only half the rate of antihypertensive and hyperglycemic drugs \([14]\). Also examining two outcomes, any initial fill within 30 days and the 180-day PDC, Raebel et al. noted that diabetes and hyperlipidemia scripts failed twice as often as medications for hypertension \([18]\). Shah et al. found that oral diabetic medications, biguanide and sulfonylurea (11% and 14%, respectively) were filled far more often than insulin (26%) \([20]\). Examining eight different oral oncolytics, Streeter et al. documented poor adherence rates ranging from 6.2% (capecitabine) to 27.2% (sorafenib) \([17]\). One article focused upon a single drug class, so no comparison across...
medications was conducted [23]. While Gleason et al. focused on the role of copayments, they
did briefly explore drug class interactions with cost, finding less price sensitivity for multiple
sclerosis agents than with tumor necrosis factor blocker [15]. Storm and colleagues directed their
analysis to selected health conditions rather than drug class, though noticed the diagnoses
associated with lowest initial adherence (e.g., psoriasis and eczema) tended to have topical drug
applications [22].

Broadly considered, medical comorbidities, illness severity, and disease chronicity was
also examined in 12 of the papers. Factors negatively influencing adherence included patients
with a greater number of physical illnesses [16], a higher Charlson comorbidity score [21],
experiencing a recent acute myocardial infarction or heart failure [28], a greater number of health
system contacts within six months prior to the initial fill [19], and having currently elevated A1c
or blood pressure levels [20]. In addition, patients having chronic conditions such as diabetes
[25] or, for example, psoriasis rather than an acute skin infection [22], individuals experiencing
current serious symptoms such as asthma exacerbations, severe coughing, or pneumonia [9], and
patients self-reporting either long-term illnesses in general or fair to poor overall health status
[10, 11], tend to display worse primary adherence behavior. Kessler et al. explored the
interaction between pharmacy copayments and ten different diagnoses, observing that
prescriptions for asthma and rhinitis were most sensitivity to medication cost while diabetes,
epilepsy, and hypertension drugs were affected the least [26]. Similarly, while also concentrating
on pharmacy naïve patients and their medication costs, Solomon also looked at a limited set of
conditions. The authors found that higher copayments led to sharper declines in refills for
hypertension and high cholesterol drugs (27% and 29% drop, respectively) than for diabetes
medications (11% drop) [27]. Examining a separate but related issue, perhaps another proxy for illness burden, the number of medications taken by a patient was positively related to lower adherence, such as a greater quantity prior to a myocardial infarction as described by Jackevicius and colleagues [24], or for oral oncology adherence in general [17]. However, Raebel et al. found that patients receiving fills in multiple drug classes actually were more likely to better initially adherent [18].

Pharmacy copayments or out of pocket medication expenses, reported in 11 articles, represented perhaps the strongest association with poor initial adherence. Although two studies observed no or minimal adherence differences by copayment status [14, 19], others documented a significant influence of medication cost upon initial fill behavior. Gleason et al., reported a strong linear effect across several copayment levels, ranging from about a 5% failed initiation rate for patients paying <$100 up to over 25% as cost exceeded $500 for expensive specialty drugs [15]. For oncology medications, a comparable copayment range led to a four-fold difference in adherence [17]. Summarizing a detailed analysis by Kessler et al., copayment level was significantly associated with early treatment termination ranging from 1-40% as out of pocket costs increased [26]. First-fill adherence problems were consistently seen in several others studies, rates nearly doubling when patients faced even $10 copayments [7, 20, 21]. The risks were substantial greater in prescriptions with attached to $40 or $50 (adandonment odds ratios of 3.5 to 4.5 compared to fills with no copayment cost [16]. Two additional studies [27, 30] did not directly look at copayments, instead analyzing the effects of a multi-tiered pharmacy benefits system as a proxy for different patient medication costs, with similar findings that patients utilized fewer non-preferred drugs.
Another broad category combined here for presentation was the influence of medication beliefs or provider relationships. Yood and colleagues observed that initial adherence rates for osteoporoses nearly doubled in patients believing the medication was effective, along with an understanding that their condition was serious and warranted treatment [12]. In a randomized trial, Raue et al. determined that patients offered treatment strongly congruent with their preferences and effectiveness beliefs (whether medication, therapy, or no care), had much better prescription initiation and 4-month adherence rates [8]. A low sense of general trust in the healthcare system overall was associated with up to 3.5 times the likelihood of poor adherence, with older patients experiencing worse problems [10]. Wroth & Pathman also found that poor adherence was strongly associated with dimensions of trust and the therapeutic alliance, including a lacking confidence in their doctor’s ability to help them, and low satisfaction with the quality of care provided [11]. In addition, Shrank et al. point out that patients tended to avoid non-preferred medications in their study, another expression of treatment preferences [16]. Also described to some extent in five studies, certain physician characteristics were correlated with lower initial adherence, such as scripts written by a trainee, resident, junior or younger physician [7, 22, 25]. Prescriptions written by inpatient cardiology specialists were filled more frequently [24], yet on the outpatient side, those originating from primary care physicians were filled more often than patients seeing specialist providers [19].

Poor clinical response to treatment, either from past patient experiences or the very first course of a new prescription, was found to be negatively associated with early adherence [9, 14]; not surprisingly, medication side effects also reduced the likelihood of adherence, thought this was directly examined in only one study [9]. A variety of other factors associated with initial
adherence were noted, infrequently presented but contributing to the information pool. These included a lower likelihood for electronic prescriptions to be filled [16], along with scripts written on the weekend or those sent to an outside pharmacy [7]. Patients receiving discharge medication counseling were tended to initiate treatment more often [24], as were individuals receiving a prescription from emergency room visits rather than a routine clinic appt [22]. Diabetic patients who smoked [19], those prescribed antidepressants without a clear mental health diagnosis [23], and patients lacking transportation [11] were nearly twice as likely to be poorly adherent. Finally, patients with either insurance coverage other than an HMO and those with shorter coverage periods prior to the initial fill were seen to have worse primary adherence [19].

**Insert Table 3 (?) about here**

Discussion

Acknowledgements:

This research was supported by ISPOR … The views expressed in this article are those of the authors and do not necessarily represent the views of ISPOR and the individual institutions of the authors.
References

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2. Pharma Insight, Patients take more power over prescription decisions [Wolter Kluwer Pharmaceuticals], 2010.


Table 1: Final List of Primary Adherence Publications Meeting Inclusion Criteria (n=24) – **JZ finishing …**

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<th>Sample Size (Patients or RXs)</th>
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<tr>
<td>van Geffen et al., 2009 [23]</td>
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<tr>
<td>Wamala et al., 2007 [10]</td>
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<tr>
<td>Yood et al., 2008 [12]</td>
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</tbody>
</table>
Table 2: Key Adherence Terminology for the 24 Eligible and 39 Ineligible Fully Reviewed Publications

Table X Key Term Usage for the 24 Eligible and 39 Ineligible Fully Reviewed Publications,

<table>
<thead>
<tr>
<th>Compliance Terms</th>
<th>Key Adjectives</th>
<th>Initial</th>
<th>First-Fill</th>
<th>Early</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Any</td>
<td>3%</td>
<td>46%</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td>Adherence</td>
<td>0%</td>
<td>33%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Abandonment</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Redemption</td>
<td>0%</td>
<td>8%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Persistence</td>
<td>0%</td>
<td>4%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Additional text from Craig: Further, it was the only term that when used in conjunction with a compliance term uniquely identified an eligible publication as its use in the one ineligible publication was with therapy (i.e. primary therapy), which is not a compliance term. Initial was the second most commonly used term, observed in 42% (10 of 24) of the eligible publications, but it was almost as common at 38% in the ineligible. First-Fill was the third most commonly used term, being used almost 4 times as frequently in eligible publications than in the ineligible (38% vs. 10%). Abandonment and redemption were the only key compliance terms that were
exclusively associated with eligible articles, however, adherence was used exclusively in eligible articles when associated with first-fill.
## Table 3: Behavioral Risk Factors Frequently Associated with Poor Initial Adherence

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th># of Times Reported</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics / Patient Characteristics</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>12</td>
<td>7, 10, 11, 13, 16, 17, 21-25, 30</td>
</tr>
<tr>
<td>Socioeconomic Status</td>
<td>8</td>
<td>10, 11, 16, 17, 19, 24, 28, 30</td>
</tr>
<tr>
<td>Gender</td>
<td>4</td>
<td>11, 13, 16, 25, 30</td>
</tr>
<tr>
<td>Race / Ethnicity</td>
<td>3</td>
<td>11, 19, 23</td>
</tr>
<tr>
<td>Rural Residency</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Drug Class / Specific Medication</td>
<td>12</td>
<td>7, 13-18, 20-26, 29, 30</td>
</tr>
<tr>
<td>Medical Comorbidities, Illness Severity, and Disease Chronicity</td>
<td>12</td>
<td>9-11, 16, 19-21, 22, 25-28</td>
</tr>
<tr>
<td>Pharmacy Copayments / Out of Pocket Medication Expenses</td>
<td>11</td>
<td>7, 14-17, 19, 20, 21, 26, 27, 30</td>
</tr>
<tr>
<td>Medication Beliefs or Provider Relationships</td>
<td>5</td>
<td>8, 10-12, 16</td>
</tr>
<tr>
<td>Physician Characteristics</td>
<td>5</td>
<td>7, 19, 22, 24, 25</td>
</tr>
<tr>
<td>Poor Treatment / Side Effects</td>
<td>2</td>
<td>9, 14</td>
</tr>
<tr>
<td>Miscellaneous Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electronic Prescriptions</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Weekend Scripts / Outside Pharmacy</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>discharge medication counseling</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Prescription from Emergency Room</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Antidepressants without Mental Health DX</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Patients Lacking Transportation</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>non-HMO Insurance Plan</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Shorter Insurance Coverage Period</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Flow Chart of study design / search process

Potentially relevant publications identified by search terms N = 865

Excluded following review of title and key words N = 558

Publications reviewed in full N = 63

Excluded by initial review and discussion of abstracts N = 243

further exclusions

• no primary data (3)
• did not examine Primary or Initial Adherence (36)

Final eligible articles N = 24