# The Role of Trust and Hope in Antipsychotic Medication Reviews in Primary Care Settings: A Realist Review.

**Lisa Marie Grünwald** ( lisa.gruenwald.17@ucl.ac.uk )
University College London
**Claire Duddy**
University of Oxford
**Richard Byng**
Plymouth University
**Nadia Crellin**
Nuffield Trust
**Joanna Moncrieff**
University College London

**Research Article**

**Keywords:** primary care, general practice, antipsychotic medication, medication review, Severe Mental Illness (SMI), schizophrenia, psychosis, stigma, trust, Shared Decision Making (SDM)

**Posted Date:** February 25th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-236325/v1



**Version of Record:** A version of this preprint was published at BMC Psychiatry on August 4th, 2021. See the published version at https://doi.org/10.1186/s12888-021-03355-3.

## Abstract

**Background:** Increasing number of service users diagnosed with schizophrenia and psychosis are being discharged from specialist secondary care services to primary care, many of whom are prescribed long-term antipsychotics. It is unclear if General Practitioners have the confidence and experience to appropriately review and adjust doses of antipsychotic medication without secondary care support.

**Aim:** To explore barriers and facilitators of conducting antipsychotic medication reviews in primary care for individuals with no specialist mental health input

**Design & Setting:** Realist review in general practice settings.

**Method:** A realist review has been conducted to synthesise evidence on antipsychotic medication reviews conducted in primary care with service users diagnosed with schizophrenia and/or psychosis. Following initial scoping searches and discussions with stakeholders, a systematic search and iterative secondary searches were conducted. Articles were systematically screened and analysed to develop a realist programme theory explaining the contexts (C) and mechanisms (M) which facilitate or prevent antipsychotic medication reviews (O) in primary care settings, and the potential outcomes of medication reviews.

**Results:** Antipsychotic medication reviews may not occur for individuals with only primary care medical input. Several, often mutually reinforcing, mechanisms have been identified as potential barriers to carrying out meaningful reviews, including low expectations of recovery for people with severe mental illness, a perceived lack of capability to understand and participate in medication reviews, linked with a lack of information shared in appointments between GPs and Service Users, and perceived risk and uncertainty regarding antipsychotic medication and illness trajectory.

**Conclusions:** The review identified reciprocal and reinforcing stereotypes affecting both GPs and service users. Possible mechanisms to counteract these barriers are discussed, including realistic expectations of medication, and the need for increased information sharing and trust between GPs and service users.


## Introduction

People with a diagnosis of schizophrenia or psychosis are often prescribed long term antipsychotic medication and treated in specialist secondary care services. However, people are now increasingly discharged to primary care and thus no longer have access to specialised care. In the UK, it is estimated that approximately 30% of people diagnosed with SMI are under primary care only (1–3). Recently, this may have increased further, with some NHS trusts advising community mental health teams to discharge as much as 20% of their caseload to primary care due to the Covid -19 pandemic.

There is significant literature on shared care agreements between secondary and primary care services to provide treatment for this population, however little focuses on those people who are discharged from secondary care. This paper specifically aims to investigate the medication reviews of those people diagnosed with schizophrenia and/or psychosis, who no longer receive support from secondary care services.

In the UK, the Quality and Outcomes Framework requires a yearly health review for those on the SMI register, which should include the review of antipsychotic medication. There is however a paucity of research exploring the actual processes and content of antipsychotic medication reviews in primary care. Guidance also recommends that patients should be “on the lowest possible dose” (4) to avoid adverse reactions, however it is also unclear how this is to be achieved in primary care. This research is important, as studies have indicated that GPs feel that anti-psychotic medication prescribing is beyond their remit, and studies report a lack of knowledge and confidence in prescribing this medication (5). Audits have also highlighted issues with current antipsychotic prescribing, including polypharmacy, dosages above BNF limits and off-label prescriptions (6,7).

Antipsychotic medication deserves specific attention, as it is the main treatment for people with psychosis or schizophrenia. It is effective in reducing psychotic symptoms and reducing the risk of relapse, but it is also associated with serious side effects, including sedation and reduced motivation (8), sudden cardiac death (9), cardiovascular disease (10) and possibly decreased brain volume (11,12) and cognitive impairment (13). Although long-term prescribing has been the norm for decades, there is also a good rationale to suggest that not everyone requires long-term treatment or derives more benefit from it than harm (14,15).

Therefore, antipsychotic medication should be reviewed regularly and appropriately to ensure that it is prescribed appropriately. This may be particularly pertinent for primary care only patients, who are on average older, on more medication and have been diagnosed for longer than service users (SU) still under secondary care(2,3). Reducing antipsychotic medication should be one of the options considered, since this has the potential to lower the risk of cardiovascular events and to reduce immediate side effects and thus improve quality of life. Such decisions need to balanced against risks of relapse and suicide. It is unclear as to how primary care clinicians should be best supported in such important decisions. The extent to which GPs feel they can have discussions about antipsychotic medication in this population is unclear, especially given the lack of guidance available on what constitutes an appropriate medication review (7,16).

# Aim

The aim of this study is to explore “what works, for whom, in what respects, to what extent and in which context”, for medication reviews conducted in primary care for SUs diagnosed with SMI. Specifically, we explored potential barriers and facilitators to conducting comprehensive medication reviews from a GP and SU perspective.

## Method

A realist review was conducted to permit exploration of the underlying factors which might influence medication reviews in primary care and the development of a testable, explanatory framework (programme theory), which could guide further research in this area (17). This synthesis produced realist 'context-mechanism-outcome configurations' (CMOCs) that describe and explain the contexts and mechanisms likely to generate important outcomes relating to antipsychotic medication reviews (17; please see Figure 1 for the process flow chart).

Realist methodology is a theory driven approach, used to assess complex evidence relating to the implementation of policy, programmes, services and interventions (17). It is concerned with understanding context in relation to underlying mechanisms of action and aims to address the key question: what works, for whom, under what circumstances and how? (as opposed to simply, "does it work?") (17). For this review, the stages outlined by Pawson (2006) were followed, as well as the Realist And Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES) guidelines (18,19).

The full protocol is available elsewhere (Prospero CRD42018107573). The stages of the review process were as follows: 1) focusing the scope, 2) searching for evidence, 3) document selection, 4) data extraction and 5) data synthesis (17). Step 1 was informed by discussions with stakeholders, including the local Clinical Commissioning Group (CCG), GPs, and psychiatrists and following a presentation at Lived Experience Advisory Panel (LEAP) group and a scoping search.

Following these discussions, the topic area for this review was narrowed down, to focus on GP and primary care only patients' medication reviews, leaving out, for example, consideration of the factors affecting SUs making or attending appointments, and communication with, or prescribing done previously in secondary care settings, as these were considered not to directly influence the content of a medication review and were therefore considered beyond the remit of this review. Documents that included data relating to GP views of secondary care were still included, as early discussions indicated that these views may play a role in the conduct of medication reviews for primary care only service users.

For step 2, a systematic search of 11 databases was conducted to identify studies containing relevant data for analysis. Medline (via HDAS), EMBASE (via HDAS), The Cochrane Library, CINAHL (via HDAS), PsycINFO (via HDAS), PsycEXTRA, the Web of Science Core Collection, Scopus, IBSS, OpenGrey and PubMed (via HDAS) were searched in August 2018. Search terms included variations of terms for "antipsychotic medication" and "primary care". Initial scoping searches indicated a paucity of papers specifically discussing antipsychotic medication management in primary care, so the search strategy for the main search was designed to maximise sensitivity, and reduce the risk of missing data related to any potential contexts or mechanisms ("Big Bang Approach"; (20). Search results and results from the initial scoping searches were screened for eligibility based on the criteria in Table 1. Citation searches were run in April 2019.

The synthesis of data extracted from documents identified by the main and citation searches suggested that stereotypes and stigma were important mechanisms, therefore a further non-exhaustive, search was conducted in August 2019 using relevant search terms to identify additional evidence related to these mechanisms (full search strategy please see additional file 1).

For step 3 (document selection), all papers were screened by LG, first by title and abstract, and then in full text, with a 10% random subsample screened in duplicate by CD.

***Table 1:*** *Inclusion and exclusion criteria*

| Inclusion criteria | Exclusion criteria |
|---|---|
| **Adults (age 18 and above)** | Service users currently under section (Mental Health Act, Forensic, Community Treatment Order) or currently in crisis or studies discussing Crisis services (Home Treatment Team etc) |
| **Diagnosis of Psychosis, schizophrenia, psychosis like symptoms (SMI)** | Animal studies |
| **Medication reviews, care and treatment of service users diagnosed with SMI** | Physical health reviews only, which do not include factors around treating SU or have medication reviews alongside |
| **Published after 1954 (year the first antipsychotic was introduced)** | Studies discussing prescription of non-antipsychotic medications |
| **Published in English language** | Studies from low- and middle-income countries |
| **All study methodologies** | Studies discussing the prevalence, and treatment of side effects by adding other (non-antipsychotic) medications |
| **Prescription of antipsychotic medication in primary care** | Studies discussing the prevalence or validity of a diagnosis of severe mental illness |
| | Off – label prescribing |
| | Excluded later:<br>· Studies investigating bipolar disorder<br>· Clozapine |

All included documents and data were critically appraised and assessed for rigour and relevance in a 2-step process:

1. Overall quality appraisal (Additional Files 2) assessing the extent to which each document contributed *relevant* data (relating to contexts, mechanisms or outcomes) and assessing each document for *rigour* overall (using the Mixed Methods Appraisal Tool (21) or CASP Systematic Reviews (22), where possible).
2. Individual CMOC appraisal (Additional File 3) assessing the set of documents that contributed data to each CMOC in relation to their *relevance* to each CMOC (as each document contributed to CMOCs to a different extent) and *rigour*, i.e. the quality of their contribution to the CMOC (as each included document may have contributed a different type of data).

The results of the quality appraisal process are detailed in full in the additional files, to provide transparency with regards to each CMOCs' evidence base.

For steps 4 and 5, included documents were read in full and coded by LG, with a 10% random subsample coded in duplicate by CD. All included papers from full text screening were added to NVivo (version 12.6.; qualitative data analysis software) and were initially coded into descriptive categories, which could shed light on potential contexts, mechanisms or outcomes. As the review progressed, data codes were iteratively refined, and explanatory CMOCs were developed on the basis of the coded data. Further searching was used to identify additional documents that contained data used to refine the developing theories, as described above.

The process of refining the programme theory involved appraising and juxtaposing data extracted from the included documents. The developing analysis and explanatory CMOCs were discussed with stakeholders and refined further on the basis of their feedback. The CMOCs together allowed formation of an overall explanatory framework or "Programme Theory" (PT) which was tested and refined throughout the review through these processes of data triangulation. This overall framework describes identified barriers and facilitators to discussions about antipsychotic medication during GP appointments. Once the final PT was developed, another round of data extraction was completed to ensure that no data were missed.

## Results

A total of 55 papers were included in this review (for details, please see Figure 2 for the literature search results, Table 2 for a summary of papers identified. A full list of included papers is available in Additional File 4). No studies or guidelines directly exploring the needs of GPs or primary care only SU with respect to antipsychotic medication were found, despite a comprehensive search, illustrating the lack of research in this area. In particular, little evidence was found in relation to facilitators of antipsychotic medication reviews. The quality of included studies was variable, please see Additional File 2 and 3 for assessment of relevance and rigour for the following results.

Following the analysis steps as listed above, initial programme theories focused heavily on GPs' lack of knowledge and training (23–26), however most SU will know that their GP has limited training and the important thing is to be heard and referred at the right time (27). Difficulties in adhering to standards were also noted in physical health (1,5,28,29), suggesting that this may possibly not be related to a lack of mental health knowledge and training alone. A lack of mental health guidance was also considered to be a potentially important factor, however, even where there was guidance available, it was not well adhered to, as seen in rates of polypharmacy for example (7,30).

Other factors, like the low frequency of SMI diagnoses and complex medication regimes in this population were excluded from the initial programme theory, as these are unamenable to change. Similarly, institutional barriers were considered to potentially play a role. Stakeholder discussions identified that GPs cannot easily identify which of their SU are primary care only, and which are also under secondary care. Although this is likely to influence the initiation of conversations about medication, it cannot be changed readily. Following the scoping searches, practice nurses were also excluded from the review, as they did not seem involved centrally (3), although there should definitely be scope to be involved as recommended in the literature (31) and by the LEAP members.

***Table 2*** *Search results*

| | |
|---|---|
| **Source identification** | 30 articles main search, 20 citation search, 5 iterative searches |
| **Design** | 34 empirical studies (largely questionnaires and qualitative interviews), 1 systematic review, 16 non-systematic literature reviews, 4 other |
| **Topic** | 27 care and treatment of people diagnosed with SMI (of which 10 guidance for GPs, 7 GP surveys on treatment of people diagnosed with SMI), 21 experience of taking antipsychotics from SU perspective, 7 stigma and Shared Decision Making |
| **Country** | 31=UK, 10 = USA, 7= Australia, 3 = Canada, 1=Ireland, 1=Italy, 1= Israel, 1 =Switzerland, 1= Austria |
| **Locus of care** | 23 = primary care, 5= secondary care, 26 = about care or treatment in general, without specifically looking at service provision in secondary or primary care services, 2= n/a - setting unrelated to mental health |

Through synthesis of the data, five CMOCs were developed, describing potential barriers to antipsychotic medication reviews in primary care:

1. Low expectations regarding recovery from mental illness (1,5,25–27,29,32–55)
2. Perceived lack of SUs' capabilities to participate in medication reviews (1,7,27,32,34,39–41,47,49,50,53,55–65)
3. Lack of information sharing between GPs and SU (1,5,24,28,32,38–40,42,49,55,59,61,62,65–70)
4. Perceived risk of SUs (25,34,36–38,42,48,49,53,54,56,71–75)
5. Mutual uncertainty regarding medication and illness trajectory (1,4,5,38,43,44,47,50,55,62,72,76)

They illustrate potential explanations for a lack of conversation about, or appropriate review of antipsychotic medication in SUs diagnosed with schizophrenia or psychosis. They are not mutually exclusive: more than one, or none may characterise any particular situation, and each may occur to a lesser or greater extent (77). These findings are summarised in Table 3 alongside illustrative excerpts of the data that was used to develop the CMOCs.

**Table 3 -***Barriers and facilitators to antipsychotic medication reviews*

| Barriers | Group | CMOC | Key quote | Facilitator |
|---|---|---|---|---|
| **1. Low expectations** | GP | If GPs have low expectations regarding recovery for SU diagnosed with SMI(C), and rely on antipsychotics as a main treatment (C), then they may be left feeling hopeless (M), leading to little or no ongoing antipsychotic medication reviews (O). | "the most significant obstacles to the effective management of the chronically mentally ill are the prevailing negative attitudes and believes about them"(51) - *author* | Realistic expectations of what the medication can achieve(38,58,62), attempt to improving QoL (47,59) |
| | Service users (SU) | If GPs communicate hopelessness to SU (C), they may in turn feel hopeless (M), and therefore unlikely to commence a conversation about medication(O). | "When I approached my GP, he [..] said, 'Well, you'll be on these tablets for the rest of your life,[…] being told I'd never be able to work again, I'd never have an education, never have relationships, never have anything in my life. So, for a period of time I thought well, there's no hope" (27) – *SU focus group* | Recovery orientated treatment (74) |
| **2. Perceived lack of capabilities** | GP | Despite years of stability (C), GPs may expect SU to lack capabilities and/ or "insight" (C). If SU are perceived in this way (M) , which may be emphasised by antipsychotic side effects (apathy, cognitive impairment, C), then GPs may dismiss medication queries (M), or act in a paternalistic/authoritarian way (M), preventing Shared Decision Making (O) and a conversation regarding medication(O). GPs feel pressure to prescribe, which further adds to this (C ).Diagnostic overshadowing may also contribute to this further. (C) | GPs scepticism towards reliability and insight of people with psychosis may discourage clients themselves from help-seeking, with further negative effects on their health" (54) – *author*<br><br>"I've had difficulty in getting full regular medical check-ups as every symptom is considered a sign for stress" (42) -*SU interviews* | See SU as capable; enable SU to discuss medication/ side effects; notion that medication queries are justified (38,39,79,81) |
| | SU | In turn, experiencing a dismissal of their queries (C), particularly if SUs have a history of coercion and sectioning(C), will lead to decreased trust (M) in GPs, leading SU to not discuss medication with their GP (O)and covert medication changes (O). | I think it's just a general disregard for they have for anything that people say, because they're mentally ill therefore you know, anything they say is questionable [..] and they say, well, I have a problem with chlorpromazine or something, they might override that, rather than listen to what the consumer is saying "(84) – *SU interview* | Feel listened to, taken seriously, time to talk (39,79) |
| **3. Lack of information sharing** | GP+SU | <u>Information about medication:</u><br><br>Due to a lack of information (C), SU may be unaware (M) of the risk associated with antipsychotics and the need for check-ups, leading to no conversation (O) and lack of attendance at reviews (O). | 55% [of patients] said that they were unaware of the potential metabolic side-effects of atypical antipsychotic medications [..]61% said that they had had no monitoring blood tests in the past year. 69% did not know that certain monitoring blood tests were recommended.(28) – *SU response to survey* | Provide sufficient information (28,38,59,67,88) |
| | GP | <u>Information about side effects:</u><br><br>GPs may fear (M) that SU will discontinue their medication (O) if they are aware of side effects (C), and feel it is in the SUs interest (M) to not share sufficient information regarding side effects (O). | "At one time…it was…if you tell patients about side effects, they won't take the medication."(70) – *pharmacist interview* | Increased information sharing can lead to higher adherence and facilitates trust (55,84) |
| | SU | Due to lack of discussion about side effects (C), SU may in turn feel shocked (M) and loss of trust (M), when they experience side effects (O) which may lead them to discontinue medication without further consultation (O).<br><br>Distrust (M) is potentially amplified when SU access information elsewhere (C), like the internet, and realise that those are potentially common side effects. | "Lack of communication about antipsychotics was the contributing factor to my stopping attempt. I recall vividly when I was sitting on the couch, watching TV, and I looked down and I noticed my chest was wet, upon further inspection I realized that I was lactating. I was shocked, scared, and terrified. It was at that moment that I decided to quit." (59)– *SU interview* | Access to sufficient information could help to increase SU confidence to commence conversations about medication (57) |
| **4.Perceived risk** | GP | Despite evidence to the contrary, GPs may consider SUs to be a risk to others (C), which can lead to fear in GPs (M), which may then lead to avoidance of medication reviews (O), or GPs taking a passive role (O). | A survey of GP attitudes to people diagnosed with schizophrenia found that they endorsed either "partially true" or "completely true" for: "people are frightened by them (93.9%) and 'they would become dangerous if they stopped their medication' (73.9%). (54)– *GP responses to survey* | Notion that SU are perceived as riskier than they are (53)<br><br>Research needed to explore how to increase GPs feeling safe in appointments. |
| | SU | If SU feel that they are perceived as frightening (C), then a good GP-SU relationship or open conversation is unlikely to occur (O). | SU "felt their GP was scared of them, ending a consultation quickly and suggesting they find a different GP" (42) – *SU interview* | Feel comfortable at their GP practice, reassurance regarding risk of being sectioned. |

| Barriers | Group | CMOC | Key quote | Facilitator |
|---|---|---|---|---|
| **5. Uncertainty regarding medication and illness trajectory** | GP | If GPs worry (M) about relapses and lack confidence in changing medication, then they may be reluctant to change medication (O) for those SU who are stable in mental health (C). A lack of guidance and (perceived) secondary care support can further contribute to this (C). | Many GPs are reluctant to reduce these without supervision, especially when the patient appears well. […] There is no clear agreement on the optimum frequency for reviewing maintenance treatment, nor is there consensus on what symptom-free period warrants consideration of discontinuation. (1) - *author* | Guidance on how to review and reduce (if indicated), secondary care support (1,38) |
| | SU | SU may feel equally concerned (M) to start a conversation about medication (O), due to fears of relapse (M), especially for those who have a history of sectioning (C). SU may not even be aware that medication changes are possible (C) | "This dynamic [power imbalance] resulted in some participants feeling coerced into taking medication and out of control. [..]When the option to discontinue neuroleptic medication was not explicit, participants were left with uncertainty regarding the level of support they could expect from clinicians. […] All participants acknowledged the risks of withdrawing neuroleptic medication(38). - *SU interviews* | Continuity of care; building of trusting relationship to enable discussion of medication changes and to identify and manage potential relapse (49,55,79) |

## Discussion

### Summary

This review set out to determine which factors influence antipsychotic medication reviews in primary care. Using realist review methodology, an extensive search of the literature identified documents including data that was used to develop several CMOCs. Taken together, the CMOCs indicate the ways in which prevalent stereotypes can impede antipsychotic medication reviews. These include:

1) low expectations of people with SMI and their recovery resulting in a lack of conversations started due to hopelessness,

2) the perception that SU lack the capabilities and "insight" required to manage their illness, leading SU to feel dismissed and not taken seriously in appointments.

3) a lack of information from both GPs and SU. GPs may not share sufficient information regarding medication risks and side effects due to fears of SU stopping medication. Equally, SU may not share all information regarding their current dose and symptoms due to fears of coercion and sectioning.

4) the perception that SU pose a risk, preventing a trusting GP – SU relationship to form and

5) mutual understandable concerns regarding antipsychotic medication changes, due to the potential for relapse and uncertainties regarding effects of dose reduction, resulting in avoidance of reviewing antipsychotic medication.

### Programme Theory

The evidence reviewed suggested several factors that are relevant to whether appropriate medication reviews are conducted with individuals with schizophrenia or psychosis. Firstly, it identified a lack of communication between SU and GPs in relation to antipsychotic medication. Attribution theory suggests that stereotypes held by clinicians and SU can change their behaviour towards each other (56,78). GP expectations of lack of capacity or "insight" for example can lead to paternalistic attitudes, which prevent properly informed discussions about treatment, and do not facilitate participation of the individual in the decision-making process. The review findings evidence this, as well as the need for aspects of the therapeutic relationship, like hope and trust, to counter some of those mechanisms. Increased trust has been associated with a better therapeutic alliance (38,49,55,57,79). Given that there are multiple types of antipsychotics and dosing options, varying responses to antipsychotic medication, and no guidelines on how to review and reduce medication (16), GPs and SU encounter many uncertainties. Managing these uncertainties together requires a trusting relationship between GP and SU (55,57). Any history of coercion or sectioning under the Mental Health Act can make developing and maintaining trust more difficult, but a trusting relationship is key to shared decision making (24,79). Given the power imbalance between SU and GPs, and often held view that "doctor knows best" (79) the onus might be on the GP to start the conversation.

### Strength and Limitations

This review has benefited from the input of a diverse stakeholder group, including GPs, psychiatrists and a Lived Experience Advisory panel (LEAP). This input helped ensure that the views of these groups informed the focus of the review, and the development and refinement of the programme theory. The data included in this review was found in documents identified by a comprehensive literature search strategy, including sensitive searches in a wide range of databases and the inclusion of additional material via citation chaining. The review has been conducted and reported following the RAMESES standards (18,19).

The review's findings are limited by the availability of data used to develop the CMOCs presented above. For example, no CMOCs were identified in relation to balancing risks of reducing versus continuing medication, or in relation to best methods for tapering medication (potentially important personal and clinical challenges with regards to medication), highlighting the need for further research in this area. Many of the included studies focused on specific contexts and outcomes, providing little data relating to mechanisms, or on why the outcomes they included were found. Although several included studies addressed the

care of SU with a diagnosis of schizophrenia or psychosis in primary care specifically, none have researched a primary care only population. As a result, the findings are applied with caution to this population.

This review should be viewed as an initial model, which has identified several CMOCs which require further testing and refinement. The evidence found for this review reflects GPs and SUs self-reported actions and feelings, but whether is impacts their behaviour in a consultation is not clear (48). It is of course possible that even despite the above listed stereotypes, that practice is not affected, or affected in ways not described above.

The review also has a UK focus, and some findings may not apply to countries where GPs do not act as “gate-keepers” to secondary or specialist care.

### Comparison with existing literature

The review did not identify any existing literature, practice guidelines or interventions assessing the treatment and care of SU who are under primary care only. Previous research found that when comparing patient records, primary care only SU are older, have fewer GP appointments and are on more medication overall (2,3). The content of antipsychotic medication reviews, as well as their feasibility in primary care, have not been investigated. A focus group study of SU diagnosed with SMI was conducted in primary care (27), however SU were not explicitly primary care only, therefore it is difficult to estimate their treatment experiences and expectations, since they may differ if they are no longer under secondary care. A recent systematic review also identified expectations of low capabilities, lack of trust and paternalism (including the decision to limit the amount of information regarding adverse effects shared and “doctor knows best” mentality; (80) as barriers to patient involved prescribing.

Previous literature cites negative symptoms like apathy and paranoia, as well as cognitive difficulties associated with a diagnosis of SMI, as a reason for lack of engagement with health services in this population (5,81). The above listed CMOCs offer additional explanations, alongside potential solutions to improve engagement in the future. A recent study on lifestyle interventions to reduce cardiovascular risk also found that primary care health professionals described people as “threatening or scary or difficult” (p7, (82). This prevented staff from offering interventions. These results align with the findings of this review and illustrate the impact stigma still has on service provision. Clearer guidance is needed to address issues around (perceived) risk management in this population.

More research is urgently needed to address this gap in knowledge regarding primary care only SUs’ individual needs and treatment, as well as how GPs can be better supported to look after a population estimated to include approximately 30% of all SU with a diagnosis of schizophrenia or psychosis (2,3). This research should include studies linking patient-level data from primary care with secondary care patient records, to establish exact numbers of primary care only SU, and compare the demographics and potentially unique needs of this population, as well as research exploring SU and GP views on receiving or providing antipsychotic medication reviews solely in primary care.

### Implications for research and/or practice

Several recommendations for practice can be made on the basis of this review’s findings. Increasing GP knowledge regarding antipsychotic treatment could help GPs to develop their confidence to balance risks and benefits and make changes to medication, like reducing doses to improve side effect burden. Greater familiarity with the recovery agenda may help GPs to appreciate the possibilities of living a fulfilling life with and without medication, to counter some of the hopelessness identified in CMOC 1.

To combat some communication difficulties (as seen in CMOC 2), GPs need to enable SU to express their views (79,81) and take SU concerns seriously (39). This may also include structured assessments, as SU may not volunteer problems with their medication (2). SU complaints and queries regarding antipsychotic medication should be assumed to be justified and need proper consideration. Such ways of working are established best practice in consultation in primary care (83) but may be less common when working with individuals with psychosis. Conversations about medication should include sufficient information about antipsychotic medication (CMOC 3), and side effects as well as benefits. Increasing SU awareness of potentially severe side effects has been associated with increased trust between SU and GP (55,79) and allows SU to prepare for side effects and return to the GP for help if they persist or cause problems. Engagement with physical health monitoring may also increase, if SU are aware of the specific reasons for this (CMOC 3), which may tackle some health disparities between this population and the general population (66). This may also help to avoid SU discontinuing medication without consultation. Some evidence suggests that pharmacists can help to increase knowledge (70,84). This could ease the pressure of time limited appointments. Access to sufficient information could help to increase SU confidence to commence conversations about medication (57), improve adherence (62,68), patient safety (72) and facilitate Shared Decision Making (SDM; (58)). A more nuanced knowledge of risk would be beneficial (CMOC 4). Whereas there are certain risks associated with a SMI diagnosis, like higher rates of substances abuse, these are not as great as perceived by the general population (53), and SU have been found to be 14 times more likely to be victims of violent crime than being the perpetrator (85). A safe environment needs to be developed for GPs and SU alike.

Concerns about relapse are understandable (CMOC 5) but should not necessarily exclude attempts to reduce the dose of antipsychotic medication slowly and carefully to facilitate patient choice and minimise side effects and health complications. Continuity of care has been highlighted as a crucial factor for this population (49,79) as it can help GPs to potentially spot signs of relapse early and offer appropriate support, and is likely to be an important factor in facilitating a safe process of medication change. Continuity may also increase SU trust and encourage the start of conversations about medication. Trust could also facilitate safer prescribing (55), as SU may tailor their dose of medication, without necessarily consulting their doctor (84) and may be reluctant to disclose this due to fears of being sectioned/coerced.

Better guidance on safe reduction and discontinuation of medication(16), with a specific focus on whether this is achievable in primary care is needed, as well as better links between primary and secondary care services, as GPs do not seem to feel supported (5,26,86,87). Knowing that support is available may increase GP confidence.

Putting these recommendations in place could be a start to strengthening trust and commencing conversations, to enable appropriate and safe prescribing, whilst also maximising quality of life.

## Abbreviations

| | |
|---|---|
| BNF | British National Formulary |
| C | Context |
| CMOC | Context-Mechanism-Outcome Configuration |
| CCG | Clinical Commissioning Group |
| GP | General Practitioner |
| M | Mechanism |
| O | Outcome |
| PPI | Patient Public Involvement |
| PT | Programme Theory |
| QoF | Quality Outcome Framework |
| QoL | Quality of Life |
| SDM | Shared Decision Making |
| SMI | Severe Mental Illness |
| SU | Service User |

## Declarations

**Funding –** LG is funded by North East London NHS Foundation Trust. CD is funded by a National Institute of Health Research (NIHR) Research Methods Programme Systematic Review Fellowship (NIHR-RM-SR-2017-08-018). RB is supported by the NIHR Applied Research Collaborative (ARC) for the South West Peninsula.

The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

**Ethical approval – n/a**

**Consent for Publication - n/a**

**Availability of data and materials-** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing Interests – n/a**

**Author Contribution** LG, CD, NC,RB, JM made substantial contributions to the conception and design of the work, LG and CD made substantial contributions to the analysis and interpretation of the data, LG drafted the work and LG, CD, NC, RB and JM substantively revised it. All authors read and approved the final manuscript.

**Acknowledgements**

Dr Matteo Pizzo for his feedback on the initial manuscript, the LEAP panel for RADAR study for their feedback on the initial framework

## References

1. Burns T, Kendrick T. The primary care of patients with schizophrenia: A search for good practice. Br J Gen Pract. 1997;47(421):515–20.
2. Kendrick, Burns, Freeling, Sibbald. Provision of care to general practice patients with disabling long-term mental illness: A survey in 16 practices. Br J Gen Pract. 1994;44(384):301–5.
3. Reilly S, Planner C, Hann M, Reeves D, Nazareth I, Lester H. The role of primary care in service provision for people with severe mental illness in the United Kingdom. PLoS One. 2012;7(5).
4. Taylor D, Barnes T, Young A. The Maudsley prescribing guidelines in psychiatry. John Wiley & Sons; 2018.
5. Jones R, Major B, Fear C. Schizophrenia in a Primary Care Setting. Curr Psychiatry Rep. 2015;17(10):31–4.
6. Raynsford J, Dada C, Stansfield D, Cullen T. Impact of a specialist mental health pharmacy team on medicines optimisation in primary care for patients on a severe mental illness register: A pilot study. Eur J Hosp Pharm . 2020;27(1):31–5.

7. Mortimer AM. Atypical Antipsychotics as First-Line Treatments for Schizophrenia. Dis Manag Heal Outcomes. 2004;12(3):169–79.
8. Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry [Internet]. 2004;6(Suppl 2):3–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16001094%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC487011
9. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009;360(20):2137.
10. Foley DL, Morley KI. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Arch Gen Psychiatry. 2011;68(6):609–16.
11. Moncrieff J, Leo J. A systematic review of the effects of antipsychotic drugs on brain volume. Psychol Med. 2010;40(9):1409–22.
12. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev. 2013;37(8):1680–91.
13. Husa AP, Rannikko I, Moilanen J, Haapea M, Murray GK, Barnett J, et al. Lifetime use of antipsychotic medication and its relation to change of verbal learning and memory in midlife schizophrenia - An observational 9-year follow-up study. Schizophr Res [Internet]. 2014;158(1–3):134–41. Available from: http://dx.doi.org/10.1016/j.schres.2014.06.035
14. Murray RM, Quattrone D, Natesan S, Van Os J, Nordentoft M, Howes O, et al. Should psychiatrists be more cautious about the long-term prophylactic use of antipsychotics. Br J Psychiatry. 2016;209(5):361–5.
15. Morrison AP, Hutton P, Shiers D, Turkington D. Antipsychotics: Is it time to introduce patient choice? Br J Psychiatry. 2012;201(2):83–4.
16. Gupta S, Cahill JD. A prescription for “deprescribing” in psychiatry. Psychiatr Serv. 2016;67(8):904–7.
17. Pawson R. Evidence-based policy: a realist perspective. Sage; 2006.
18. Greenhalgh T, Wong G, Westhorp G, Pawson R. Protocol - Realist and meta-narrative evidence synthesis: Evolving Standards (RAMESES). BMC Med Res Methodol. 2011;11.
19. Wong G, Greenhalgh T, Westhorp G, Pawson R. Development of methodological guidance, publication standards and training materials for realist and meta-narrative reviews: the RAMESES (Realist And Meta-narrative Evidence Syntheses – Evolving Standards) project. Heal Serv Deliv Res [Internet]. 2014;2(30):1–252. Available from: http://dx.doi.org/10.3310/hsdr02300
20. Booth A, Briscoe S, Wright JM. The “realist search”: A systematic scoping review of current practice and reporting. Res Synth Methods. 2020;11(1):14–35.
21. Hong Q, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, et al. Mixed Methods Appraisal Tool (MMAT) Version 2018: User guide. McGill [Internet]. 2018;1–11. Available from: http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch/127916259/MMAT_2018_criteria-manual_2018-08-01_ENG.pdf%0Ahttp://mixedmethodsappraisaltoolpublic.pbworks.com/
22. CASP Critical Appraisal Skills Programme. CASP Systematic Review Critical Appraisal Checklist. 2018;(2018):1–4. Available from: https://casp-uk.net/wp-content/uploads/2018/01/CASP-Systematic-Review-Checklist_2018.pdf
23. Baker E, Gwernan-Jones R, Britten N, Cox M, McCabe C, Retzer A, et al. Refining a model of collaborative care for people with a diagnosis of bipolar, schizophrenia or other psychoses in England: a qualitative formative evaluation. BMC Psychiatry. 2019;19(1):1–17.
24. Boardman GH, McCann T V., Clark E. Accessing health care professionals about antipsychotic medication related concerns. Issues Ment Health Nurs. 2008;29(7):739–54.
25. Rasmussen J. Improving practice. Drugs Context [Internet]. 2006;2(13):589–99. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L44842250%5Cnhttp://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=17451981&id=doi:&atitle=Improving+practice&stitle=Drugs+Context&title=Drugs+in+Context&volume=2&issue=13&spage=589&epage
26. Toews J, Lockyer J, Addington D, McDougall G, Ward R, Simpson E. Improving the management of patients with schizophrenia in primary care: Assessing learning needs as a first step. Can J Psychiatry. 1996;41(10):617–22.
27. Lester HE, Tritter JQ, Sorohan H. Patients’ and health professionals’ views on primary care for people with serious mental illness: Focus group study. Br Med J. 2005;330(7500):1122–6.
28. Feeney L, Mooney M. Atypical antipsychotic monitoring: A survey of patient knowledge and experience. Ir J Psychol Med. 2006;23(3):100–2.
29. Lambert TJR, Newcomer JW. Are the cardiometabolic complications of schizophrenia still neglected? Barriers to care. Med J Aust. 2009;190(4 SUPPL.):2–5.
30. Patel MX, Bishara D, Jayakumar S, Zalewska K, Shiers D, Crawford MJ, et al. Quality of prescribing for schizophrenia: Evidence from a national audit in England and Wales. Eur Neuropsychopharmacol [Internet]. 2014;24(4):499–509. Available from: http://dx.doi.org/10.1016/j.euroneuro.2014.01.014
31. Millar E, Garland C, Ross F, Kendrick T, Burns T. Practice nurses and the care of patients receiving depot neuroleptic treatment: views on training, confidence and use of structured assessment. J Adv Nurs [Internet]. 1999;29(6):1454–61. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=107209307&site=ehost-live
32. Morant N, Kaminskiy E, Ramon S. Shared decision making for psychiatric medication management: beyond the micro-social. Health Expect. 2016;19(5):1002–14.
33. Rogers A, Campbell S, Gask L, Sheaff R, Marshall M, Halliwell S, et al. Some National Service Frameworks are more equal than others: Implementing clinical governance for mental health in primary care groups and trusts. J Ment Heal. 2002;11(2):199–212.
34. Royal College of Psychiatrists. Mental illness : stigmatisation and discrimination within the medical. 2001. 1–40 p.
35. Hustig HH, Norrie PD. Managing schizophrenia in the community. Med J Aust. 1998;168:186–91.
36. Dixon RP, Roberts LM, Lawrie S, Jones LA, Humphreys MS. Medical students’ attitudes to psychiatric illness in primary care. Med Educ. 2008;42(11):1080–7.

37. Schulze B. Stigma and mental health professionals: A review of the evidence on an intricate relationship. Int Rev Psychiatry. 2007;19(2):137–55.
38. Geyt G Le, Awenat Y, Tai S, Haddock G. Personal Accounts of Discontinuing Neuroleptic Medication for Psychosis. Qual Health Res. 2017;27(4):559–72.
39. Lambert TJR, Chapman LH, Bell S, Carr N, D'Emden M, Elsom S, et al. Diabetes, psychotic disorders and antipsychotic therapy: A consensus statement. Med J Aust. 2004;181(10):544–8.
40. Pereira S, Pinto R. A survey of the attitudes of chronic psychiatric patients living in the community toward their medication. Acta Psychiatr Scand [Internet]. 1997;95(6):464–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1997193220
41. Tranulis C, Goff D, Henderson DC, Freudenreich O. Becoming Adherent to Antipsychotics: A Qualitative Study of Treatment-Experienced Schizophrenia Patients. Psychiatr Serv. 2011;62(8):888–92.
42. Pilgrim D, Rogers A. Mental health service users' views of medical practitioners. J Interprof Care. 1993;7(2):167–76.
43. Kendrick T, Burns T, Freeling P. Randomised controlled trial of teaching general practitioners to carry out structured assessments of their long term mentally ill patients. Bmj. 1995;311(6997):93.
44. Mortimer A., Shepherd C., Rymer M, Burrows A. Primary care use of antipsychotic drugs: An audit and intervention study. Ann Gen Psychiatry. 2005;4(1).
45. Galon P, Heifner Graor C. Engagement in primary care treatment by persons with severe and persistent mental illness. Arch Psychiatr Nurs. 2012;26(4):272–84.
46. Donlon PT. The schizophrenias: medical diagnosis and treatment by the family physician. J Fam Pract. 1978;6(1):71–82.
47. Morrison P, Meehan T, Stomski NJ. Living with antipsychotic medication side-effects: The experience of Australian mental health consumers. Int J Ment Health Nurs. 2015;24(3):253–61.
48. Lawrie, Martin, McNeill, Drife, Chrystie, Reid, et al. General practitioners' attitudes to psychiatric and medical illness. Psychol Med. 1998;28(6):1463–7.
49. Lester H, Tritter JQ, England E. Satisfaction with primary care: The perspectives of people with schizophrenia. Fam Pract. 2003;20(5):508–13.
50. Johnson DAW, Rasmussen JGC. Professional attitudes in the UK towards neuroleptic maintenance therapy in schizophrenia. Psychiatr Bull. 1997;21(7):394–7.
51. Jones LR, Knopke HJ. Educating Family Physicians To Care for the Chronically Mentally Ill. 1987;24(2):177–83.
52. Viron M, Baggett T, Hill M, Freudenreich O. Schizophrenia for primary care providers: How to contribute to the care of a vulnerable patient population. Am J Med [Internet]. 2012;125(3):223–30. Available from: http://dx.doi.org/10.1016/j.amjmed.2011.05.002
53. Katschnig H. Psychiatry's contribution to the public stereotype of schizophrenia: Historical considerations. J Eval Clin Pract. 2018;24(5):1093–100.
54. Magliano L, Strino A, Punzo R, Acone R, Affuso G, Read J. Effects of the diagnostic label "schizophrenia", actively used or passively accepted, on general practitioners' views of this disorder. Int J Soc Psychiatry. 2017;63(3):224–34.
55. Maidment ID, Brown P, Calnan M. An exploratory study of the role of trust in medication management within mental health services. Int J Clin Pharm. 2011;33(4):614–20.
56. Corrigan PW. Mental Health Stigma As Social Attribution. Clin Psychol- ogy—Science Pract. 2000;(7):48–67.
57. Delman J, Clark JA, Eisen S V., Parker VA. Facilitators and Barriers to the Active Participation of Clients with Serious Mental Illnesses in Medication Decision Making: the Perceptions of Young Adult Clients. J Behav Heal Serv Res. 2015;42(2):238–53.
58. Roe D, Goldblatt H, Baloush-Klienman V, Swarbrick M, Davidson L. Why and how people decide to stop taking prescribed psychiatric medication: Exploring the subjective process of choice. Psychiatr Rehabil J. 2009;33(1):38–46.
59. Salomon C, Hamilton B. "All roads lead to medication?" Qualitative responses from an Australian first-person survey of antipsychotic discontinuation. Psychiatr Rehabil J. 2013;36(3):160–5.
60. Rogers A, Day JC, Williams B, Randall F, Wood P, Healy D. The meaning and management of neuroleptic medication: A study of patients with a diagnosis of schizophrenia. Soc Sci Med [Internet]. 1998;47(9):1313–23. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed6&NEWS=N&AN=28444745
61. Seale C, Chaplin R, Lelliott P, Quirk A. Antipsychotic medication, sedation and mental clouding: An observational study of psychiatric consultations. Soc Sci Med. 2007;65(4):698–711.
62. Britten N, Riley R, Morgan M. Resisting psychotropic medicines: a synthesis of qualitative studies of medicine-taking. Adv Psychiatr Treat. 2010;16(3):207–18.
63. Leucht S, Arbter D, Engel RR, Kissling W, Davis JM. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. Mol Psychiatry. 2009;14(4):429–47.
64. Usher K. Taking neuroleptic medications as the treatment for schizophrenia: A phenomenological study. Aust N Z J Ment Health Nurs [Internet]. 2001;10(3):145–55. Available from: http://onlinelibrary.wiley.com/doi/10.1046/j.1440-0979.2001.00205.x/abstract%5Cnhttp://onlinelibrary.wiley.com/doi/10.1046/j.1440-0979.2001.00205.x/full%5Cnhttp://onlinelibrary.wiley.com/doi/10.1046/j.1440-0979.2001.00205.x/pdf
65. Carrick R, Mitchell A, Powell RA, Lloyd K. The quest for well-being: A qualitative study of the experience of taking antipsychotic medication. Psychol Psychother Theory, Res Pract. 2004;77(1):19–33.
66. Crawford MJ, Jayakumar S, Lemmey SJ, Zalewska K, Patel MX, Cooper SJ, et al. Assessment and treatment of physical health problems among people with schizophrenia: National cross-sectional study. Br J Psychiatry. 2014;205(6):473–7.
67. Aref-Adib G, O'Hanlon P, Fullarton K, Morant N, Sommerlad A, Johnson S, et al. A qualitative study of online mental health information seeking behaviour by those with psychosis. BMC Psychiatry [Internet]. 2016;16(1):1–10. Available from: http://dx.doi.org/10.1186/s12888-016-0952-0

68. Mitchell AJ, Selmes T. Why don't patients take their medicine? Reasons and solutions in psychiatry. Adv Psychiatr Treat. 2007;13(5):336–46.
69. Schachter D, Kleinman I, Williams JI. Informed consent for antipsychotic medication: Do family physicians document obtaining it? Can Fam Physician. 1999;45(JUN.):1502–8.
70. Younas M, Bradley E, Holmes N, Sud D, Maidment ID. Mental health pharmacists views on shared decision-making for antipsychotics in serious mental illness. Int J Clin Pharm. 2016;38(5):1191–9.
71. Oud MJ, Schuling J, Slooff CJ, Groenier KH, Dekker JH, Meyboom-De Jong B. Care for patients with severe mental illness: The general practitioner's role perspective. BMC Fam Pract. 2009;10:1–8.
72. McDonell MG, Kaufman EA, Srebnik DS, Ciechanowski PS, Ries RK. Barriers to Metabolic Care for Adults with Serious Mental Illness: Provider Perspectives. Int J Psychiatry Med. 2011;41(4):379–87.
73. Corrigan PW, Kosyluk KA. Erasing the Stigma: Where Science Meets Advocacy. Basic Appl Soc Psych. 2013;35(1):131–40.
74. The Schizophrenia Commission. The Abandoned Illness: A Report by the Schizophrenia Commission [Internet]. 2012. London: Rethink Mental Illness. Available from: http://www.healthpromoting.com/sites/default/files/fastingsp2011.pdf
75. Dillner L. Mental health law obsolete, says inquiry. BMJ [Internet]. 1995 Jan 21;310(6973):145–6. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.310.6973.145a
76. Carr VJ, Lewin TJ, Barnard RE, Walton JM, Allen JL, Constable PM, et al. Attitudes and roles of general practitioners in the treatment of schizophrenia compared with community mental health staff and patients. Soc Psychiatry Psychiatr Epidemiol. 2004;39(1):78–84.
77. Dalkin SM, Greenhalgh J, Jones D, Cunningham B, Lhussier M. What's in a mechanism? Development of a key concept in realist evaluation. Implement Sci. 2015;10(1):1–7.
78. Corrigan P. How stigma interferes with mental health care. Am Psychol. 2004;59(7):614–25.
79. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: A systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns [Internet]. 2014;94(3):291–309. Available from: http://dx.doi.org/10.1016/j.pec.2013.10.031
80. Pedley R, McWilliams C, Lovell K, Brooks H, Rushton K, Drake RJ, et al. Qualitative systematic review of barriers and facilitators to patient-involved antipsychotic prescribing. BJPsych Open. 2018;4(1):5–14.
81. Annamalai A, Tek C. An Overview of Diabetes Management in Schizophrenia Patients: Office Based Strategies for Primary Care Practitioners and Endocrinologists. Int J Endocrinol. 2015;2015:1–8.
82. Burton A, Osborn D, Atkins L, Michie S, Gray B, Stevenson F, et al. Lowering cardiovascular disease risk for people with severe mental illnesses in primary care: A focus group study. PLoS One. 2015;10(8):1–16.
83. Pendleton D. The consultation: an approach to learning and teachingle. Oxford University Press; 1984.
84. Happell B, Manias E, Rope C. Happell_et_al-2004-International_Journal_of_Mental_Health_Nursing. Int J Ment Health Nurs. 2004;13:242–8.
85. Brekke JS, Prindle C, Sung Woo Bae, Long JD. Risks for individuals with schizophrenia who are living in the community. Psychiatr Serv. 2001;52(10):1358–66.
86. Carr VJ. The role of the general practitioner in the treatment of schizophrenia: specific issues. Med J Aust. 1997 Feb;166(3):143–6.
87. Bindman J, S. J, S. W, G. S, P. B, E. K. Integration between primary and secondary services in the care of the severely mentally ill: Patients' and general practitioners' views. Br J Psychiatry [Internet]. 1997;171(AUG.):169–74. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9337955
88. Happell B, Platania-Phung C, Scott D. Proposed nurse-led initiatives in improving physical health of people with serious mental illness: A survey of nurses in mental health. J Clin Nurs. 2014;23(7–8):1018–29.

## Figures

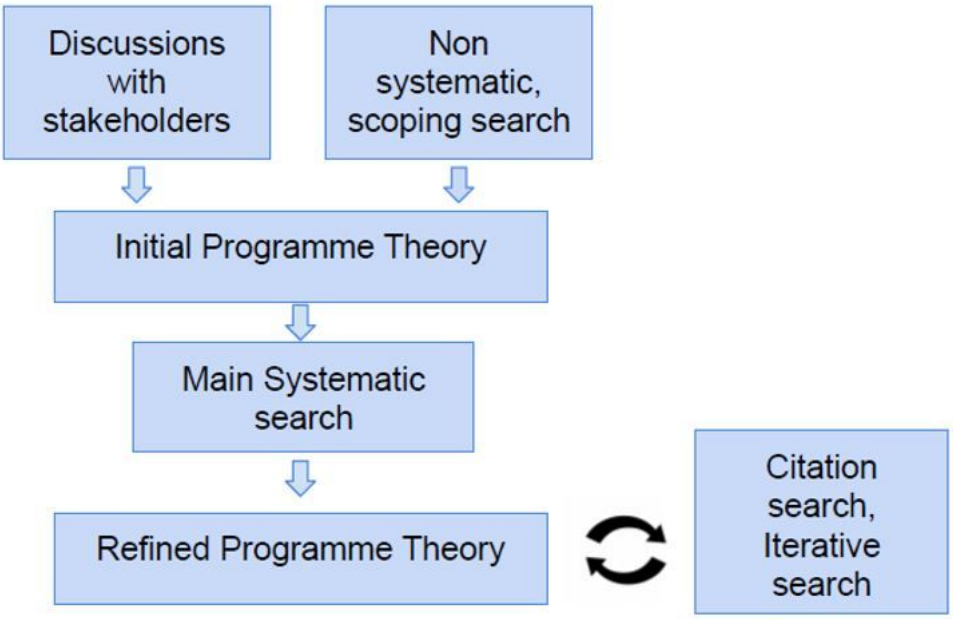


**Figure 1**

Flow Chart

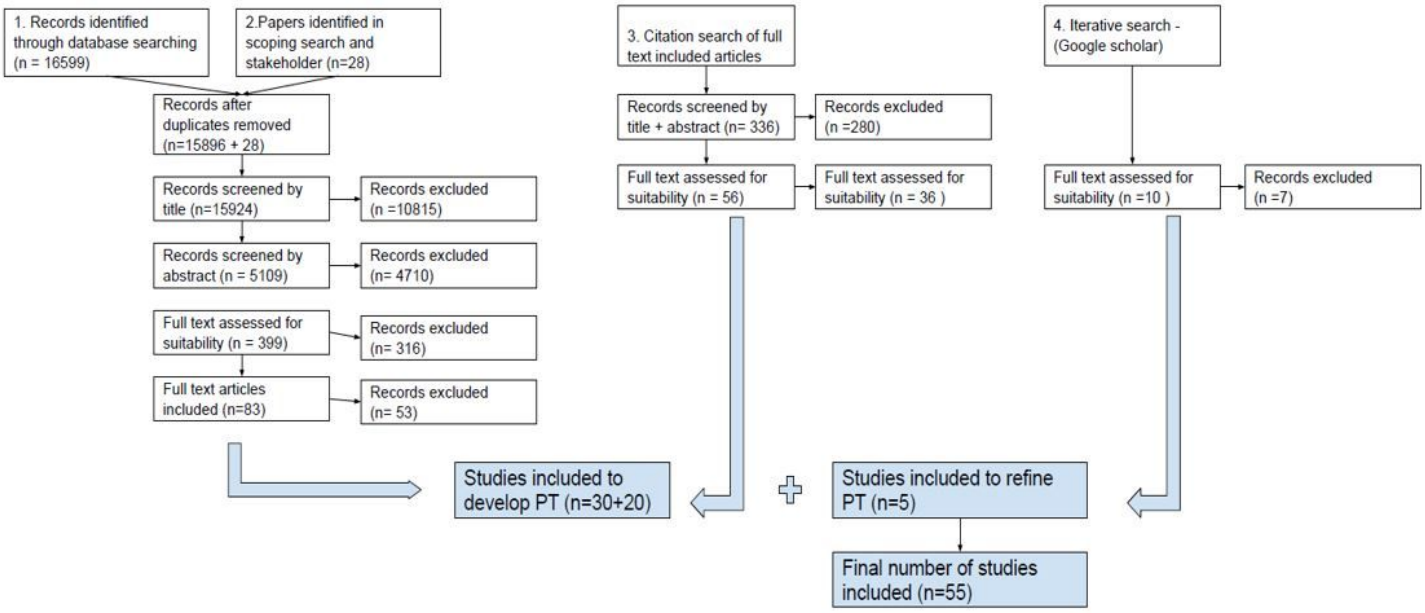


**Figure 2**

Literature Search

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFiles.docx