

A Target Product Profile and Economic Impact Assessment

for an agitation treatment for
people living with dementia

January 2022

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 **Alzheimer's
Research
UK**

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Summary



The impact

Agitation and aggression are common symptoms of dementia, including Alzheimer's disease, affecting an estimated 35-50% of people living with dementia. They have a large impact on people living with dementia and their carers and are often issues that precipitate the move into assisted living facilities.



Available treatments

There is high unmet need that exists in symptomatic treatments for people living with dementia and Alzheimer's disease. Currently, treatments for agitation in Alzheimer's disease and dementia are not very effective, can only be used for a maximum of 12 weeks, and have a number of side effects. demonstrates an opportunity to meet that unmet need.



Our approach

To help stimulate interest and investment in developing new treatments for people living with dementia, we developed a Target Product Profile (TPP) for agitation for people living with dementia. In addition to the TPP, we conducted economic modelling to show the potential impact of a future agitation treatment.

Summary - TPP for agitation

To help stimulate interest and investment in developing new treatments for people living with dementia, we developed a TPP for agitation for people living with dementia.

The TPP considers:

- Primary indication
- Target patient population
- Treatment goal
- Efficacy
- Adverse effects
- Method of administration and treatment region

The TPP also looks at how this could be evaluated considering the following factors:

- Study duration
- Clinical outcomes
- Clinical measures
- Patient, carer and clinician report outcomes measures



Summary - Economic model

We conducted economic modelling to show the potential impact of a future agitation treatment. We sought to understand the impact of a treatment that met the criteria outlined in the TPP, considering impact on quality of life, health and social service utilisation and cost.

Key findings;

- The economic modelling found that, in the absence of any new therapy, the effect of clinical agitation is:
 - to **increase discounted lifetime cost by £57,800 per person** (NHS £5,500, social care £52,300) and
 - to **reduce discounted QALYs by 1.06** (of which 0.77 is attributable to the person with dementia and 0.29 to the carer).
- Approximately 90% of the cost increase is attributable to the higher rate of admission to residential care for people with agitation.
- A hypothetical therapy that prevented the onset of clinical agitation, would be cost-effective provided that its price was less than £12,200 per patient per year (with reference to the NICE threshold of £20,000 per QALY).
- However, if the treatment reduced the incidence of clinical agitation by only 10% or 20%, its cost would need to be less than £1,200 or £2,450 per year, if it is to be regarded as cost-effective.



Project areas

Scale of dementia
and impact of agitation



Agitation
drug pipeline, current treatments and clinical guidelines



TPP
an agitation treatment for people living with dementia



Economic modelling
on the impact of this TPP treatment





Scale of dementia

and impact of agitation

Dementia is one of our **greatest medical challenges**



Dementia has **higher health and social care costs** (£11.9bn) than cancer (£5bn) and chronic heart disease (£2.5bn) combined.



Globally, the number of people living with dementia is projected to increase from **50m** in 2018 to **152m** in 2050, **a 204% increase.**



In 2018, the estimated cost of dementia globally **reached \$1 trillion** and will double to **\$2 trillion by 2030.**

Agitation has a **huge impact on people living with dementia**, but treatment options are currently limited

Agitation and aggression are a group of symptoms usually understood as purposeless behaviour such as shouting, moving about or even violence without an obvious cause. ¹

We have targeted agitation and aggression as the symptoms to address in this TPP for several reasons:



High impact:

Agitation has a large impact on people living with dementia and their carers and is often an issue that precipitates the move into assisted living facilities.



Poor existing treatments:

Currently, treatments for agitation in Alzheimer's disease and dementia are not very effective, can only be used for a maximum of 12 weeks, and have a number of side effects.



Large patient population:

Agitation and aggression are common symptoms of dementia, including Alzheimer's disease, affecting an estimated 35-50% of people living with dementia.

These factors demonstrate the high unmet need that exists in symptomatic treatments for people living with dementia and Alzheimer's disease, and it also demonstrates an opportunity to meet that unmet need.

The mainstay of drug treatment for agitation for those suffering from dementia is antipsychotic medication

Antipsychotic drugs may be prescribed for people with Alzheimer's disease, vascular dementia, or mixed dementia. However, antipsychotic drugs can cause serious side effects, and the risk increases with continued use over weeks and months.

- **Antipsychotic drugs** have low efficacy, with the American Psychiatric Association guideline group reporting they “demonstrate minimal or no efficacy with strong placebo effects” (Banerjee et al., 2021).
- **In the UK in 2009**, there were an estimated 1800 deaths and 1620 cerebrovascular adverse events attributable to the use of antipsychotics in dementia (Banerjee et al., 2021).

• **Antipsychotic drugs** also cause harm in those with dementia, including excess dementia-specific mortality. With possible side effects including shaking, unsteadiness, reduced mobility and drowsiness, or confusion (Antipsychotics and other drug approaches in dementia care, 2021).

The routine uses of antipsychotic drugs for the treatment of agitation for those suffering from dementia highlights the need for adequate symptomatic treatments, that will effectively improve the quality of life of those suffering.



Emily and her mum Janet



Emily's mum, Janet, was diagnosed with early-onset Alzheimer's disease in 2010

Emily said:

"For us as a family, my mum's agitation symptoms were one of the hardest things to deal with.

"The way it manifests in my mum is that she can't be on her own at all. She couldn't even watch TV on her own at home. She could be really calm and then all it would take was for her to realise she was on her own in the room and she'd get very distressed and angry.

"We desperately wanted to soothe her and reassure her that it would be all okay, but the only way to keep her calm would be for someone to be with her constantly.

"This put so much pressure on us, particularly my dad who was looking after her 24 hours a day.

"I would visit my mum at least once a month and the whole weekend would be spent in an intense, emotional state.

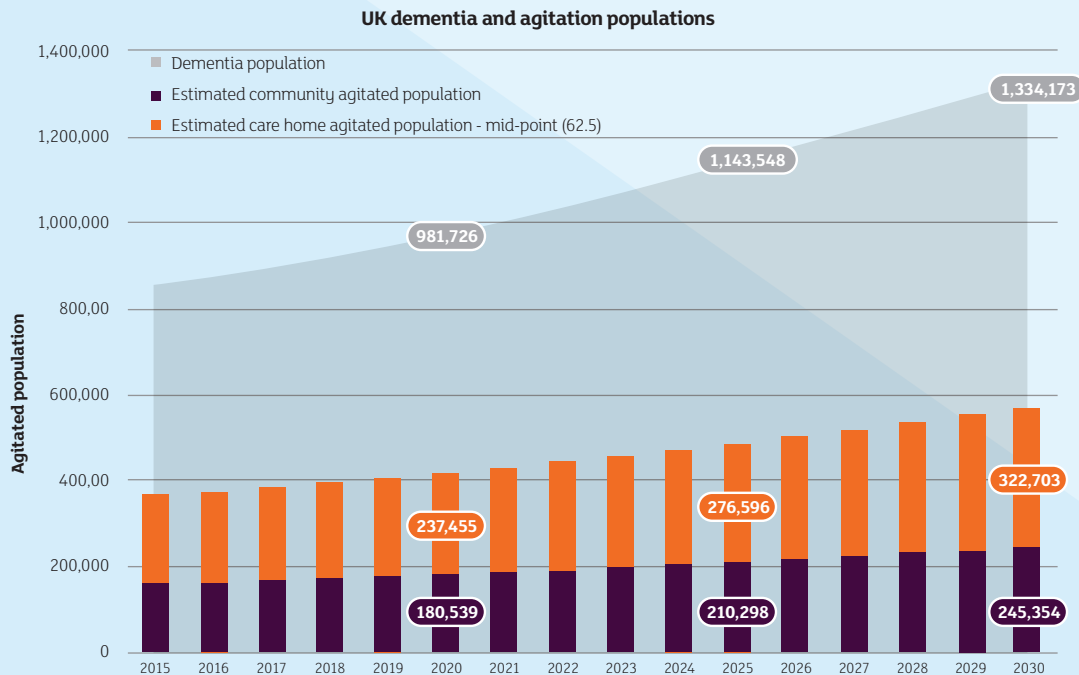
"Eventually we had to take the decision for her to go into a home as it became impossible for us to provide the care she needed.

"She's been so much calmer since she went into the home. She's always surrounded by people, so she has that comfort."

"For us as a family, my mum's agitation symptoms were one of the hardest things to deal with."



Estimated patient population of people living with dementia along with those with agitation in the community and in care homes



Key messages

- The total number of people living with dementia is expected to rise from 980,000 in 2020 to 1.3 million in 2030.
- Of these, 42.6% are expected to have symptoms of agitation.
- A greater proportion of people with dementia in care homes have agitation (40% - 85%) compared to those living in the community (30%).



Agitation

Drug pipeline, current treatments
and clinical guidelines

Current clinical guidelines on treatment of agitation

The current clinical guidelines² recommend the following treatments:

- First action if agitation or aggression presents; identify possible causes and make appropriate clinical or environmental changes e.g. pain, delirium.
- As initial and ongoing management, offer psychosocial and environmental interventions.
- Only offer antipsychotics if a risk of harm to patients or others, or if agitation, hallucinations or delusions are causing severe distress.
- In cases of dementia with Lewy Bodies; antipsychotics may worsen motor symptoms and Parkinson's disease guidance may be referred to in cases of hallucinations or delusions - clozapine may be prescribed but requires a clozapine monitoring service.
- If antipsychotics are used, lowest dose for shortest time is preferred. Benefits of antipsychotic treatment on average last between 6 and 12 weeks. Assess every 6 weeks.
- Halt medication if no additional benefit is found or after discussions with patients and carers.



Current agitation treatment options for people living with dementia

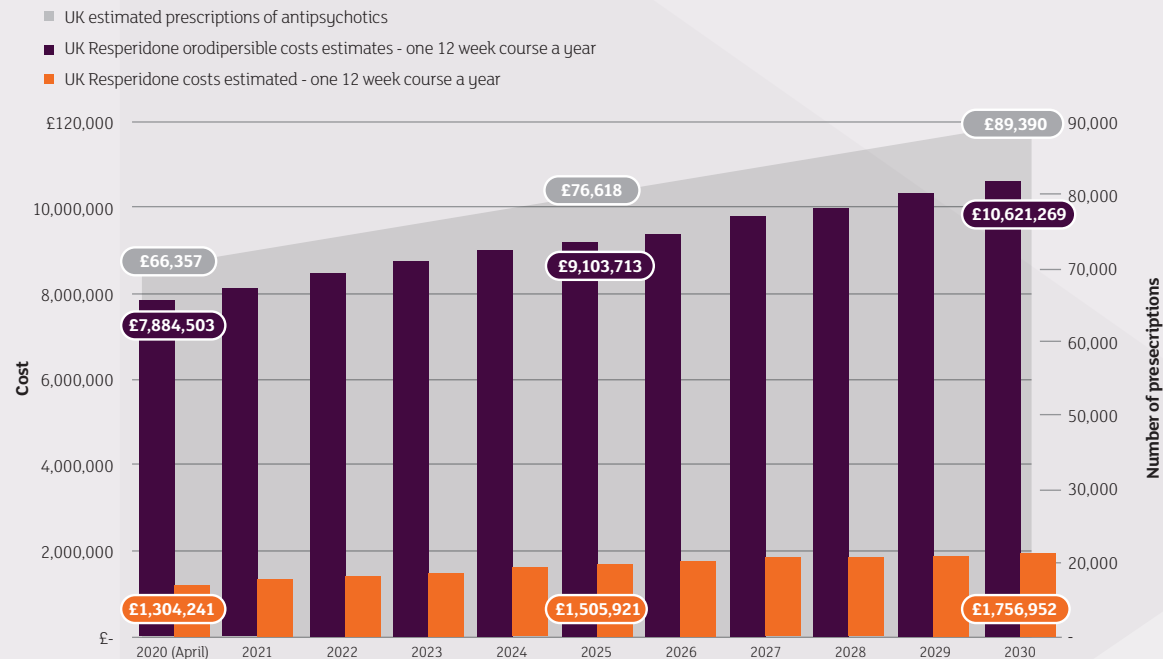
In the clinical guidance², the only antipsychotics with a UK marketing authorisation for this indication are Risperidone and Haloperidol.

- The marketing authorisation for Risperidone only covers short-term treatment (up to 6 weeks) of persistent aggression in people with moderate to severe Alzheimer's disease unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.
- The marketing authorisation for Haloperidol only covers treatment of persistent aggression and psychotic symptoms in people with moderate to severe Alzheimer's dementia and vascular dementia when non-pharmacological treatments have failed and when there is a risk of harm to self or others.



Estimated antipsychotic usage and cost

UK Risperidone cost projections to 2030
Risperidone 500mg B.D. costs from BNF used



Key messages

- Based on current England diagnosis rate and prescribing data, there will be around 2,000 additional prescriptions of Risperidone a year for people living with dementia.
- Using BNF costs and one 12-week cycle per patient, the estimated annual Risperidone cost (as of April 2020) ranges from £1.3m to £7.9m depending on the formulation.
- Currently, the majority of Risperidone use is the lower cost formulation.

Estimated prevalence, diagnoses and prescriptions for 2019 and 2020 from NHSE Recorded Dementia Diagnoses publication for 2019/20 and April 2020

Estimated prevalence for 2021-2030 from CFAS 2 and ONS 2018 population projections for England

Estimated diagnoses for 2021-2030 are set at the national diagnoses ambition of 67%

Estimated prescribing based on England April 2020 national average of 10% of those diagnosed, having a prescription for antipsychotics

All data for 65+ age group

Costs derived from NICE guidance on Risperidone use (500mg B.D.); Cost comparison charts (Jan 2020) REGIONAL DRUG AND THERAPEUTICS CENTRE for a 12 week treatment

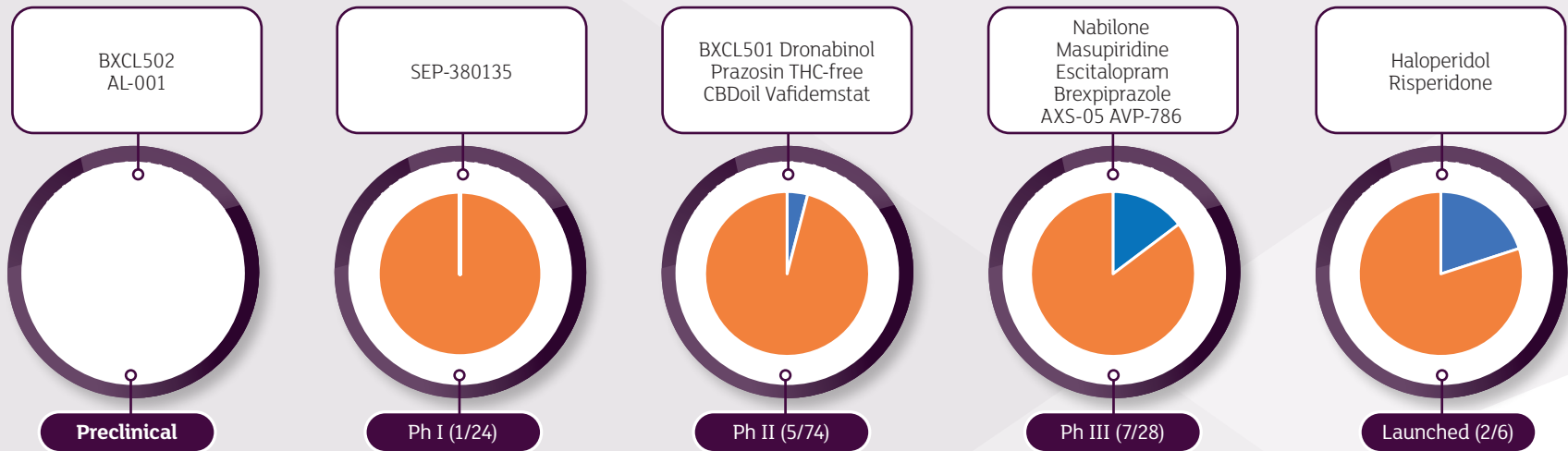
Estimates for the UK are based on England diagnoses and prescribing rates, with a UK dementia population

Current drug pipeline for agitation treatments for people living with dementia/Alzheimer's disease

Currently only a small fraction of drugs in development for Alzheimer's are aimed at addressing symptoms of Agitation. Banerjee et al., (2021) argue that anti-depressants (e.g. Mirtazapine) are not the answer.

Pipeline of drugs for the treatment of agitation in people with Alzheimer's disease as at 2021

(Pie charts: as a % of drugs at each phase of clinical development aimed at addressing Alzheimer's disease as at 2021)



■ Agitation ■ All other AD See Appendices for Molecular Mechanism of Action information

% agitation/all drugs being developed for AD taken from Cummings et. al. (2021)³ and combined with data from Global Data Drugs database 4 to reflect the live pipeline

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TPP

An agitation treatment for people
living with dementia



To outline **the ideal characteristics** of a future agitation treatment, a TPP was developed.



The following slides outline the **target patient population, efficacy, mechanism of administration and side effect goals.**



There are also recommendations around **clinical evaluation requirements**, including clinical measures and outcomes.

How the TPP was developed



Stage 1: Scoping

Research was conducted by ARUK and MDC into symptoms of dementia, focussing on those that could be treated with novel treatments.

Agitation was selected as the symptom to investigate due to its large impact on patients and carers, poor existing treatments, and viability as a target.

Data on current standard of care (including treatments), drugs in trials, and clinical assessment methods on agitation in dementia was collated from published literature and other databases to drive the next stage.



Stage 2: Consultation

Patients and carers – case studies from members of ARUK's Policy Involvement Panel are included as qualitative evidence.

Clinicians – opinions from several clinical specialties were incorporated, in both the standard of care summary and the development of the TPP.

Health economists – modelling the impact of a novel agitation treatment was commissioned from the Personal Social Services Research Unit (PSSRU; now CPEC) at LSE.



Stage 3: Synthesis

By combining the research with the perspectives of stakeholders, the TPP was iterated and refined, providing treatment goals and efficacy estimates for the economic modelling.

Using insight from industry, the revised TPP was verified with its target audience and finalised.

The final version is presented here.

The TPP

Product attribute	Product profile	Minimum requirement	Ideal requirement
Primary indication	Treatment of the signs and symptoms of agitation manifesting as excessive motor activity, verbal or physical aggression in patients with Alzheimer's disease.	Chronic treatment of the signs and symptoms of agitation manifesting as excessive motor activity, verbal or physical aggression in patients with moderate and severe Alzheimer's disease.	Chronic treatment of the signs and symptoms of agitation manifesting as excessive motor activity, verbal or physical aggression in patients with MCI or mild/moderate or severe Alzheimer's disease.
Patient population(s)	<p>Any patient with Alzheimer's disease and agitation or aggression. Example diagnostic tools below.</p> <ul style="list-style-type: none"> • Cognition and memory • MMSE, CDR, ADAS-CoG • Agitation • CMAI: Score of ≥ 39 • NPI: Product of frequency and severity on agitation dimension ≥ 4 • Clinical diagnosis of Alzheimer's disease • Alzheimer's disease according to NIA-Alzheimer's Association criteria (2011) 	<p>Patients with moderate and severe Alzheimer's dementia with agitation or aggression.</p> <ul style="list-style-type: none"> • Cognition and memory • MMSE: 0 – 20 • CDR: 2 – 3 • ADAS-CoG: >37 • Agitation • CMAI: Score of ≥ 39 • NPI: Product of frequency and severity on agitation dimension ≥ 4 	<p>Patients with Alzheimer's disease and agitation or aggression.</p> <ul style="list-style-type: none"> • Cognition and memory • MMSE: 0 – 30 • CDR: 0 – 3 • ADAS-CoG: 0 - 70 • Agitation • CMAI: Score of ≥ 39 • NPI: Product of frequency and severity on agitation dimension ≥ 4
Treatment goal	<p>Reduced frequency of agitated episodes following acute (non-prophylactic) administration.</p> <p>Reduced burden of agitation to the caregiver.</p> <p>Reduction of concomitant medications (e.g. benzodiazepines, SSRI/SNRIs or antipsychotics) to manage agitation.</p>	<p>A reduction in occurrence of agitated episodes by 30% or severity by 30%.</p> <p>Reduction of caregiver burden due to agitation by 30%.</p> <p>Reduction of concomitant medications to manage agitation.</p>	<p>No further agitated episodes following acute dosing for duration of treatment; 100% reduction.</p> <p>No further agitation burden to caregiver.</p> <p>No further use of concomitant medications to manage agitation.</p>

The TPP

Product attribute	Product profile	Minimum requirement	Ideal requirement
Efficacy	<ol style="list-style-type: none"> 1. Equal to or superior to current anti-psychotics licenced for use in managing agitation and aggression in dementia. 2. Equal to or superior treatment duration to current treatments [risperidone; a 6 – 12 week course]. 3. Equal to or shorter time to respond to treatment compared to current therapies. 	<ol style="list-style-type: none"> 1. A reduction in occurrence of agitated episodes by 30% and/or severity by 30%. 2. Sustained efficacy for a minimum of 12 weeks. 3. Time to respond within 2 weeks. 	<ol style="list-style-type: none"> 1. Agitated episodes halted following acute dosing. 2. Sustained efficacy for chronic use. 3. Time to respond less than 24 hours.
Adverse effects	<p>No adverse effects in mortality or morbidity, in short or long term.</p> <p>Side effect profile superior to current treatments, particularly related to;</p> <ul style="list-style-type: none"> • Sedation, drowsiness • Parkinsonism, shaking and unsteadiness • Increased risk of falls • Increased risk of stroke <p>Low drug-drug interactions requiring dose adjustments for other common concomitant medications in AD patients.</p> <p>Suitable for combination therapy with AChEs / memantine.</p> <p>No abuse liability (not scheduled).</p>	<p>No side effects, no adverse effects in long term or short term mortality or morbidity.</p> <p>Side effect profile not worse than current treatments;</p> <ul style="list-style-type: none"> • Incidence of gait disturbance no greater than those associated with benzodiazepine or antipsychotic usage. • Incidence of major adverse cardiovascular events (e.g. stroke) and QT elongation no greater than those associated with atypical antipsychotic usage. • Incidence of infections no greater than those associated with atypical antipsychotic usage. <p>Limited drug-drug interactions requiring dose adjustments for other common concomitant medications in AD patients.</p> <p>Suitable for combination therapy with AChEs / memantine.</p> <p>Abuse liability equal to current treatments; schedule 4 (benzodiazepines).</p>	<p>No adverse effects in mortality or morbidity, in short or long term.</p> <p>No side effects.</p> <p>No drug-drug interactions for concomitant medications for patients with Alzheimer's disease.</p> <p>Suitable for combination therapy with AChEs / memantine.</p> <p>No abuse liability (not scheduled).</p>
Administration and treatment regimen	<p>Must be suitable for patients with swallowing difficulty.</p> <p>Viable options include; Patch – QD or less frequent.</p> <p>Oral liquid/buccal spray – QD though BID is acceptable.</p> <p>Subcutaneous (SC) injection for biologics – 2-4 weekly SC injection.</p>		

The TPP

Recommendations for the purpose of clinical evaluation

Study duration	Acute treatment: 12 weeks with a run-in time [up to 6 weeks] to reduce the impact of clinical trial participation on care and symptoms. Chronic treatment: 24 weeks with a run-in time [up to 6 weeks] to reduce the impact of clinical trial participation on care and symptoms.
Clinical outcomes	Reduced frequency and/or severity of agitation episodes over the trial period. Superior adverse side effect profile than comparator.
Clinical measures	Cognition: MMSE, ADAS-Cog, CDR, CDR-SoB Agitation scales: Cohen-Mansfield Agitation Inventory (CMAI) or Neuropsychiatric Inventory (NPI) can be used; both have different forms and subscales. There is no clear consensus on which is most appropriate, though the NPI Nursing home version may be appropriate for residential care settings. Other: BEHAVE-AD
Patient and carer, and clinician reported outcome measures	Quality of life assessment for carer and patient such as DEMQoL and DEMQoL-Proxy. Improvements in one or more Clinical Global Impression (CGI) scales (patient, caregiver or clinician), including reduced caregiver strain/burden will strengthen efficacy profile.



Economic modelling

on the impact of this TPP treatment

Economic modelling - the impact of a new agitation treatment

Model development

Goal

To understand the impact of a treatment that met the criteria outlined in the TPP, economic modelling was conducted to understand the value of such a treatment, considering impact on quality of life, health and social service utilisation and cost.

Data summary

This modelling was based on data from analysis of two longitudinal studies which assessed the impact of agitation in people living with dementia, in terms of service utilisation and quality of life. The studies are:

- Modelling the outcome and cost impacts of interventions for DEMentia (MODEM)⁵
 - 307 people with dementia and their carers. The mean age of the person with dementia was 79 years of age and 47% were female. Over a year, the severity of dementia and the level of disability increased but the prevalence of agitation remained stable.
- STrategies for RelaTives (START)⁵
 - A randomised controlled trial, for both carers and people living with dementia. 196 carers contributed data at the 2-year follow-up. The mean age of the person living with dementia was 79 and 58% were female.



Economic modelling - the impact of a new agitation treatment

Impact of agitation in dementia

Summary

This analysis was based on the illustrative case of a person with mild dementia aged 75 using a Markov model with transitions from mild to moderate dementia and from moderate to severe dementia and, within each level of severity, a risk of admission to residential care and a risk of mortality.

The lifetime discounted costs were estimated along with the effects (in terms of QALYs) for people receiving a hypothetical treatment that reduced agitation in comparison with people not receiving the treatment, under various assumptions about the treatment effects.

Cost of agitation in dementia

The economic modelling found that, in the absence of any new therapy, the effect of clinical agitation is:

- to **increase discounted lifetime cost by £57,800 per person** (NHS £5,500, social care £52,300) and
- to **reduce discounted QALYs by 1.06** (of which 0.77 is attributable to the person with dementia and 0.29 to the carer).

Approximately 90% of the cost increase is attributable to the higher rate of admission to residential care for people with agitation.



Economic modelling - the impact of a new agitation treatment

Impact of a hypothetical treatment

Summary

The next stage of the modelling was to look at the impact of reducing agitation on patients, carers and the health and care sector. This was used to estimate the amount that the NHS would be willing to pay for an agitation treatment, based on the NICE threshold of £20,000 per QALY and the cost savings of reducing agitation.

Results

A hypothetical therapy that **prevented the onset of clinical agitation, would be cost-effective provided that its price was less than £12,200 per patient per year** (with reference to the NICE threshold of £20,000 per QALY).

However, if the treatment **reduced the incidence of clinical agitation by only 10% or 20%, its cost would need to be less than £1,200 or £2,450 per year**, if it is to be regarded as cost-effective.

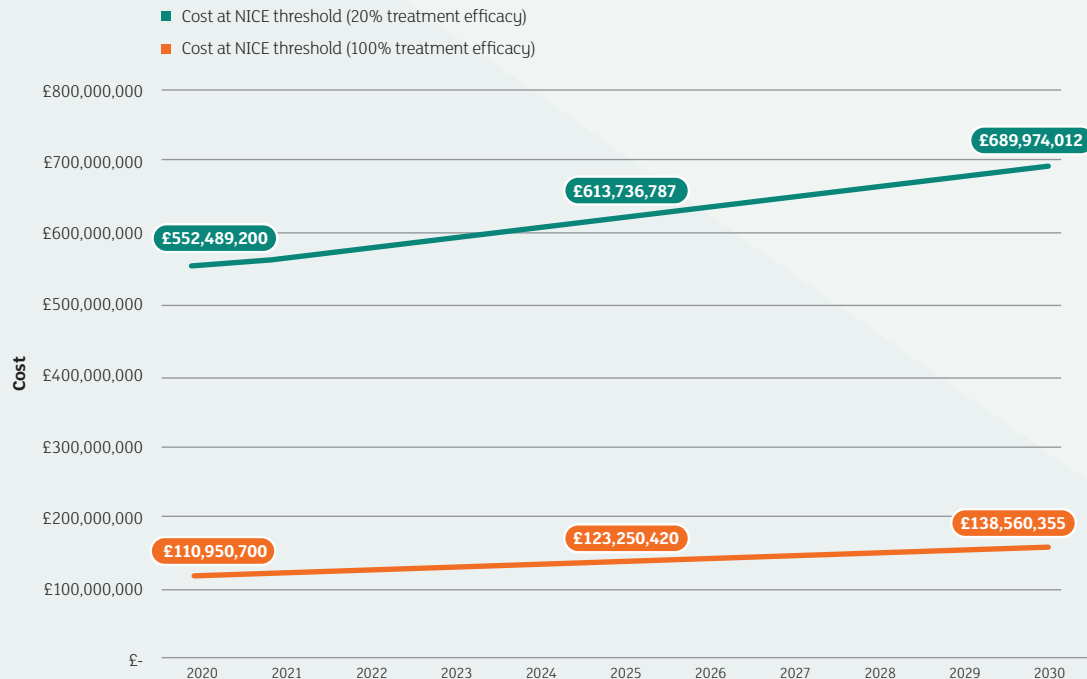
***NB:** These findings are sensitive to the data source and assumptions in the modelling, especially data on the quality of life of the person with dementia and the quality of life of the carer where the person with dementia has non-clinical agitation and is in the mild stage of the disease. It's important this is borne in mind when considering the findings.*



Estimates of cost for future agitation treatments, based on efficacy

England cost estimates of new agitation treatment

Based on Knapp et al modelling



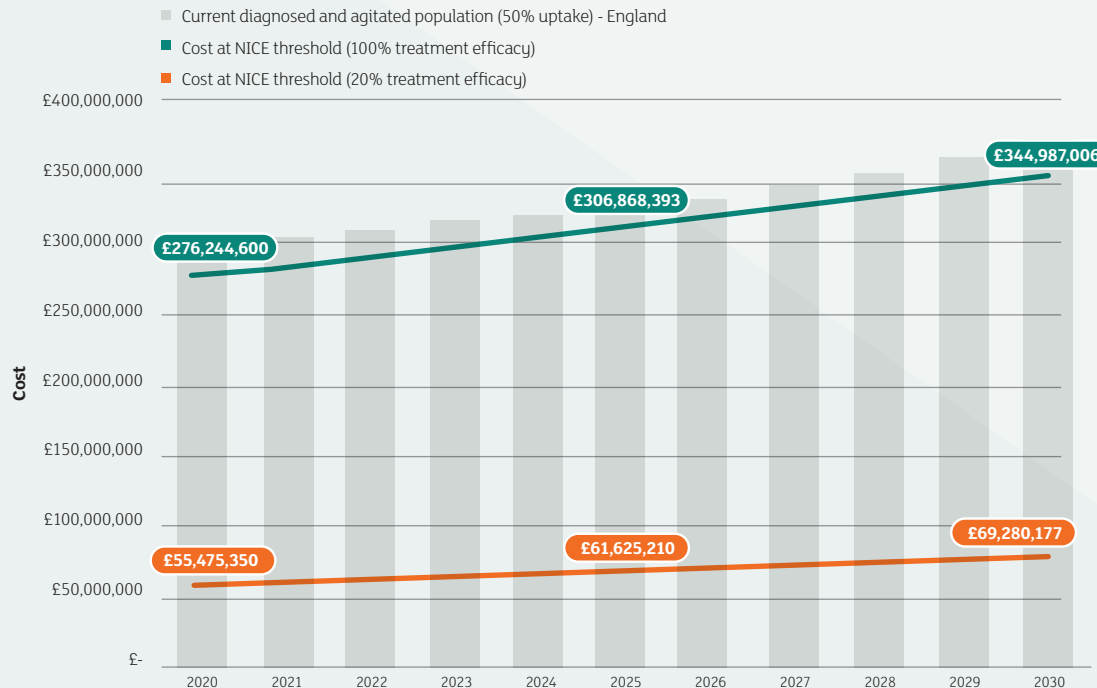
Key messages

- The NICE threshold of £20,000 per QALY and reduction in cost of care are used to determine the maximum willingness to pay, and therefore cost, of a new agitation treatment with a given level of efficacy.
- Using the population of those currently on Risperidone, at a 20% efficacy level the annual cost for a drug that meets the NICE threshold is £110m.
- The higher the efficacy of the drug, the greater its impact on agitation and the greater its value to the healthcare system.
- This only considers health and social care costs, not informal care cost.

Estimates of cost for future agitation treatments, based on efficacy

Cost-effective expenditure on new agitation treatment

Based on Knapp et al modelling⁵



*Current diagnosed and agitated population is based on current prescriptions for risperidone in England
50% uptake implies that half the existing population can use the new treatment
Cost per patient based on annual cost of drug

Key messages

- The NICE threshold of £20,000 per QALY and reduction in cost of care are used to determine the maximum willingness to pay, and therefore cost, of a new agitation treatment with a given level of efficacy.
- Using the population of those currently on Risperidone, at a 20% efficacy level the annual cost for a drug that meets the NICE threshold is £110m.
- The higher the efficacy of the drug, the greater its impact on agitation and the greater its value to the healthcare system.
- This only considers health and social care costs, not informal care cost.

Economic modelling

Additional data on quality of life

Impact of agitation on the quality of life of a person with dementia

- **MODEM:** Statistical analysis found a significant association between agitation and reduced quality of life in people with dementia at baseline using EQ-5D proxy as the QOL assessment measure. This was not the case when using DEMQOL proxy.
- The analysis did not find a statistically significant association between agitation at baseline and quality of life of the person with dementia at 12-month follow-up.

Effects of agitation on admission to residential care

- **MODEM:** Statistical analysis found that the rate of admission to residential care was higher for those with clinical agitation than for those with no or non-clinical agitation. While the annual admission rate was 6% for those with no agitation and 7% for those with non-clinical agitation, it was 20% for those with clinical agitation.
- **MODEM and START:** In a multivariable analysis people with clinical agitation appeared to have a higher probability of entering residential care than people without clinical agitation, but this relationship was not statistically significant after controlling for a range of variables including age, gender, education and disability.
- The subsamples entering residential care were, however, small, and some of the variables included in the analyses may not be wholly independent of agitation.



Economic modelling

Additional data on carer quality of life

Effects of agitation on quality of life of the carer

- **MODEM:** Analysis found a trend towards ($p=0.082$) an association between agitation and reduced carer quality of life at baseline. As with QoL outcomes for a person with dementia, analysis of carer quality of life at 12-month follow-up found no significant association with the presence of agitation at baseline.
- **START:** Analysis found a statistically significant association between clinical agitation and reduced carer self-reported QoL as measured by EQ-5D; carers rated their QoL significantly lower at the next research assessment as compared to carers of people with non-clinical agitation. Progression of agitation from being absent or non-clinical to clinical 4 months later led to an average decline of 0.04 on carer's EQ-5D values.

Effects of agitation on carer anxiety, depression and carer burden

- **MODEM:** Carers of people with clinical agitation rated their level of burden at baseline as significantly higher compared to carers of people with non-clinical agitation. Consistent with effects on carer QoL findings there was no significant association between agitation at baseline and carer burden at 12-month follow-up
- **START:** Carers of people with clinical agitation rated their anxiety and depression significantly higher at the next research assessment as compared to carers of people with non-clinical agitation. Progression of agitation from being absent or non-clinical to clinical 4 months later led to an average increase on the anxiety and depression scale of 1.4 points (42-point scale).



Economic modelling

Additional data on frequency and cost

Frequency

- **MODEM:** 21% of those living in the community at baseline had clinical agitation. Only 42% of those with clinical agitation at baseline still had clinical agitation at 12-month follow-up. Of those without clinical agitation at baseline, 15% had clinical agitation at 12-month follow-up.
- **START:** 32% had clinical agitation as assessed on the agitation item in the NPI. Two-thirds (64%) of those with clinical agitation at baseline still had clinical agitation at 4-months, 75% at 8 months, 57% at 12 months and 54% at 24 months.

Cost

- **MODEM:** Found that clinical agitation at baseline was associated with a higher likelihood of using social care at baseline that approached statistical significance ($p=0.055$) as compared to non-clinical agitation. However, analysis looking at factors associated with costs at 12-month follow-up found that agitation at baseline was not significantly associated with either use or cost of social care services. Agitation at baseline was not significantly associated with unpaid care costs at baseline or follow-up.
- **START:** Found a trend towards clinical agitation being associated with higher health and social care costs incurred by the person with dementia ($p=0.067$). However, no association was observed between agitation of the person with dementia and costs of health and social care service for carers.



Concordance with other relevant studies

Cost

Clinical agitation among people with dementia appeared to be associated with higher health and social care costs, however, the relationships were less clearly defined in our analyses than those reported in some previous studies. The studies that we drew our samples from and the type of analysis we conducted are the most likely cause of these differences.

- A systematic review of 160 papers concluded that severe agitation in people with dementia doubled health and social care costs in comparison to people without clinical agitation (Livingston et al. 2014b). Also, the costs appear to increase with increasing level of agitation (Panca et al. 2019; Costa et al. 2018).
- **Cost differences between the agitated and non-agitated group were smaller in our analysis than other studies, though still significant.**
- While our study only focussed on the health and social care costs of dementia, other studies show that informal care costs are larger than social care costs. In 2020 in the UK, the estimated cost of dementia is £31bn broken down into £5bn of healthcare costs (16%), £12bn of social care costs (39%), and £14bn of informal care costs (44%).
- **By including informal care costs as well, the impact of agitation and therefore the impact of a treatment could be significantly different. However, collecting detailed data on informal care costs specifically due to agitation is challenging.**



Considerations for future work

Frequency of agitation

- **MODEM:** 51 out of the 238 people (21%) living in the community at baseline had clinical agitation. Only 42% of those with clinical agitation at baseline still had clinical agitation at 12-month follow-up. Of those without clinical agitation at baseline, 15% had clinical agitation at 12-month follow-up.
- **START:** At baseline in the community sample, 84 out of 259 people (32%) had clinical agitation as assessed on the agitation item in the NPI. Two-thirds (64%) of those with clinical agitation at baseline still had clinical agitation at 4-months, 75% at 8 months, 57% at 12 months and 54% at 24 months.

Impact on research

In dementia, cognitive decline and quality of life degenerate progressively over time but agitation is an episodic symptom, which poses challenges for data collection in research. The MODEM study collected data at annual intervals and the START study at 4 month intervals, which could have impacted the quality of the recording as an episode of agitation is more likely to be missed. Additionally, the tests used ask respondents to record agitation in a recent time period (the previous one or two weeks), as opposed to since the previous assessment.

- **Frequent or continuous data collection, such as diaries or remote assessment, may be needed in clinical trials to provide significant results.**



Considerations for future work

Quality of life

Agitation was related to lower quality of life in people with dementia, lower quality of life of their carer, higher carer anxiety and depression, and possibly higher carer burden. In some cases, however, the relationship was statistically significant only when examining costs and outcomes contemporaneous with the report of agitation, and not when examining costs and outcomes at follow-up 4 or 12 months later, by which time the person may no longer have clinical agitation.

In addition, in MODEM, agitation was associated with quality of life when using EQ-5D proxy but not with DEMQOL proxy, confirming the importance of appropriate assessments of quality of life in dementia – an issue that has been highlighted previously (Aguirre E et al. Qual Life Res. 2016).

Impact on research

Identifying the impact on QoL of specifically agitation in a condition like dementia that has a range of symptoms poses accuracy and sensitivity challenges, further complicated by the need for proxy measures.

- **Use of agitation- or dementia-specific instruments may provide more sensitive measurement alongside EQ-5D and an increased frequency of assessment will give a clearer picture of QoL fluctuations.**



Considerations for future work

Residential care admission

In multi-variable analysis of both the MODEM and the START community samples, people with clinical agitation appeared to have a higher probability of entering residential care than people without clinical agitation, but this relationship was not statistically significant.

This finding is from analyses controlling for a range of variables including age, gender, education and disability. The subsamples entering residential care were, however, small, and some of the variables included in the analyses may not be wholly independent of agitation.

Impact on research

The high cost and long-term duration make admission to residential care a driving factor behind the cost-effectiveness of treatments. Anecdotal evidence indicates that because agitated behaviours can be challenging for informal carer to manage, agitation can be the symptom that precipitates residential care admission. A weak correlation was found in our analysis despite the main cost differences being caused by residential care.

- **Further research into the impact of agitation on residential care admission is warranted to provide information on the size of this effect and, potentially, into methods of supporting people living with dementia and their carers to remain in the community.**



Simon and his dad Ted



Simon's dad, Ted, was diagnosed with Alzheimer's disease in 2013.

Simon said:

"One of the first signs that something was wrong with Dad was that he would get increasingly aggressive at home. We would be walking on eggshells constantly as the simplest thing, even just talking to him, would set him off.

"The worst period of agitation was around three years after his diagnosis. Dad would be constantly awake in the night, tearing curtains down and pulling everything out of the wardrobes.

"Then he would constantly be looking for my mum, even though she was in the same room. He would walk around for hours shouting her name, constantly wandering in the night, switching lights on and off, looking for her.

"No matter what we did or said, it was impossible to calm him. He often would only stop once he had exhausted himself.

"It pushed me and my mum to the edge mentally. Looking back, I don't know how we coped. It was a lot of stress. Everything revolved around managing the next meltdown.

"I think a treatment to reduce agitation would enable people to look after their loved ones at home longer. It would have massively reduced the stress for both Mum caring for him and Dad himself."



About ARUK



Alzheimer's Research UK is the UK's leading dementia research charity dedicated to diagnosis, prevention, treatment and cure.



Backed by our passionate scientists and supporters, we're challenging the way people think about dementia, **bringing together the people and organisations** who can speed up progress, and investing in cutting-edge research.



We believe that medical research can and will deliver life-changing preventions, treatments and one day, a cure for dementia. **Alzheimer's Research UK exists to make this happen** and with your support, we'll make life-changing breakthroughs possible.

About MDC

Medicines Discovery Catapult is a national facility connecting the UK community to accelerate innovative drug discovery.

We're a government funded, not-for-profit organisation, and this financial independence makes us unique.

We're able to take risks and pursue objectives that are understandably challenging for commercial for-profit companies. It's the reason we're able to focus so much of our effort on pioneering the next generation of medicine discovery techniques and technologies.

By validating new ways of discovering medicines and driving key talent and expertise across the sector, we will support the UK life sciences industry, SMEs and innovators to deliver growth for the UK economy and maintain the UK's heritage position as a global leader in medicines R&D.

Ultimately, new industrialised technologies are vital for delivering new medicines to patients, faster.

md.catapult.org.uk/
[@MedDiscCat](#)





References

and further information

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Further information

- National Audit of Dementia Fourth Round 2018/19 included a special report on prescribing for people living with dementia which included anti-psychotics. Royal College of Psychiatrists <https://www.rcpsych.ac.uk/improving-care/ccqi/national-clinical-audits/national-audit-of-dementia/nad-reports-and-resources>
- Recorded Dementia Diagnoses publication (monthly). NHS Digital. <https://digital.nhs.uk/data-and-information/publications/statistical/recorded-dementia-diagnoses>





Appendices

Appendix 1:

Approved Drugs for alleviation of agitation in Alzheimer's disease

Agent Phase	Mechanism of Action	Data	Source
Risperidone	Marketed	Atypical Antipsychotic (5-HT _{2A} , D ₂ Antagonist)	https://www.medicines.org.uk/emc/search?q=risperidone
Haloperidol	Marketed	Atypical Antipsychotic (D ₂ Antagonist)	https://www.medicines.org.uk/emc/search?q=Haloperidol

Appendix 2:

Pipeline of symptomatic treatments for agitation in clinical development

Agent	Sponsor	Phase	Mechanism of Action	(Source(s
AVP-786 deudextromethorphan hydrobromide + quinidine sulfate	Avani	III	Sigma-1 R Agonist, NMDA Receptor Antagonist	Cummings (2021), GlobalData (2021)
AXS-05 Bupropion + dextromethorphan	Axsome Therapeutics	III	Sigma-1 R Agonist, NMDA Receptor Antagonist	GlobalData (2021)
Brexpiprazole	Otsuka	III	D2 R, 5HT1A partial agonist,	Cummings (2021), GlobalData (2021)
Escitalopram oxalate	NIA, JHSPH Center for Clinical Trials	III	Serotonin reuptake inhibition	Cummings (2021), GlobalData (2021)
Masupiridine	Suven Life Sciences Ltd	III	5HT6 antagonist	GlobalData (2021)
Nabilone (Cesamet)	Sunnybrook Health Sciences Center	III	Cannabinoid (receptor agent)	Cummings (2021), GlobalData (2021)
BXCL501	BioXcel Therapeutics	II	ALpha2-adrenergic receptor agonist	Cummings (2021)
Dronabinol (Marinol)	Mclean Hospital, Johns Hopkins University	II	CB1, CB2 endocannabinoid receptor partial agonist	Cummings (2021), GlobalData (2021)
Prazosin hydrochloride	The Alzheimer's Disease Coop Study (ADCS), NIA	II	Alpha-1 adrenoreceptor antagonist	Cummings (2021), GlobalData (2021)
THC-free CBD oil	Eastern Virginia Medical School, Ananda Hemp	II	Cannabinoid with effects on cannabinoid receptors	Cummings (2021)
Vafidemstat (ORY-2001)	Oryzon Genomics SA	II	LSD1 inhibitor	GlobalData (2021)
SEP-380135	Sunovian Pharmaceuticals	I	-	GlobalData (2021)

Appendix 3:

Pipeline of symptomatic treatments for agitation in preclinical development

Agent	Sponsor	Phase	Mechanism of Action	(Source(s
BXCL502	BioXcel	Preclinical	-	GlobalData (2021)
AL001- (Liprosal)	Alzamend Neuro Inc	Preclinical	Form of Lithium, GSK3A/B Inhibitor	GlobalData (2021)

Appendix 4:

Numbers of agents in development by indication

Indication	Preclinical	Ph I	Ph II	Ph III	Regulatory Approval	Launched
Agitation	-	1	5	7	-	2
All Other	-	23	69	21	-	4
Totals	-	24	74	28	-	6

Agitation vs. All other drugs to treat symptoms associated with Alzheimer's disease

Indication	Preclinical	Ph I	Ph II	Ph III	Regulatory Approval	Launched
Agitation	-	1	5	7	-	2
Other Symptomatic	-	1	5	4	-	4
Totals	-	2	10	11	-	6

Adapted from GlobalData (2021) and Cummings et. al. (2021)²

Development of the TPP – Informatics used during the scoping

