Long / Post COVID

Off-Label-Use of Drugs in Germany

Prof. Dr. med. Bernhard Wörmann

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DGHO
DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

Bundesinstitut für Arzneimittel und Medizinprodukte

AWMF
Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.

CHARITÉ

Off-Label Use

Germany

G-BA

Application by stakeholder

Off-Label Expert Commission (BfArM)

Working Group

- **External Expertise**
- **Discussion**
- **Recommendation**

Decision

Pharmaceutical Guideline (Policy)

Insurances

Individual application for cost assumption

- **Evaluation**
- **Expert opinion (Medical Service)**
- **Competence Center Oncology**

Decision

Appeal

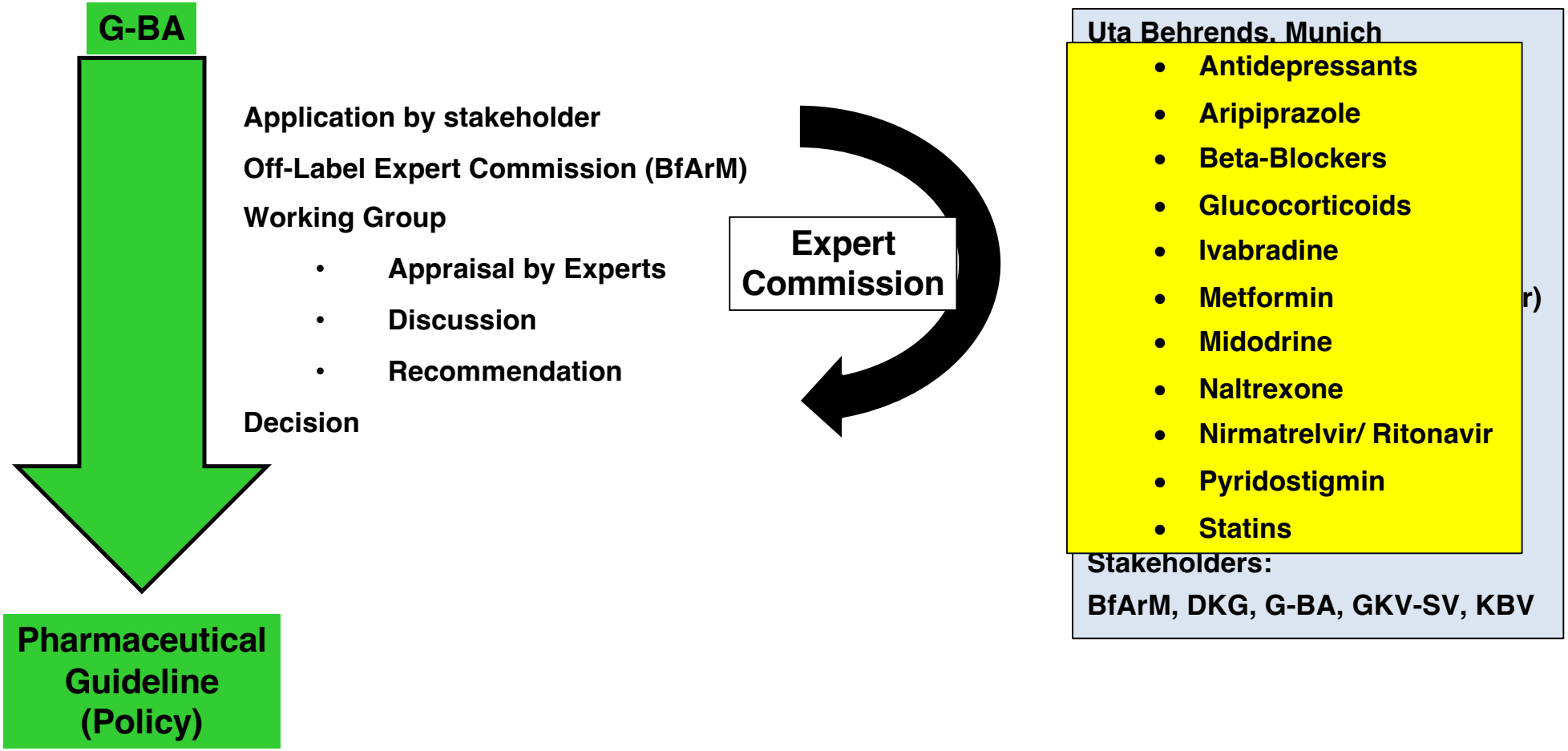
- **(Revision)**

Decision

Lawsuit

Off-Label Use

Long / Post COVID



Off-Label Use

WIG 2

Evidence Research

Pharmaceuticals

- Antidepressants
- Aripiprazole
- Beta-blockers
- Glucocorticoids
- Ivabradine
- Metformin
- Midodrine
- Naltrexone
- Nirmatrelvir / Ritonavir
- Pyridostigmine
- Statins

Research

Level 1

- Long COVID / Post COVID

and

- Symptom / syndrome

Level 2/3

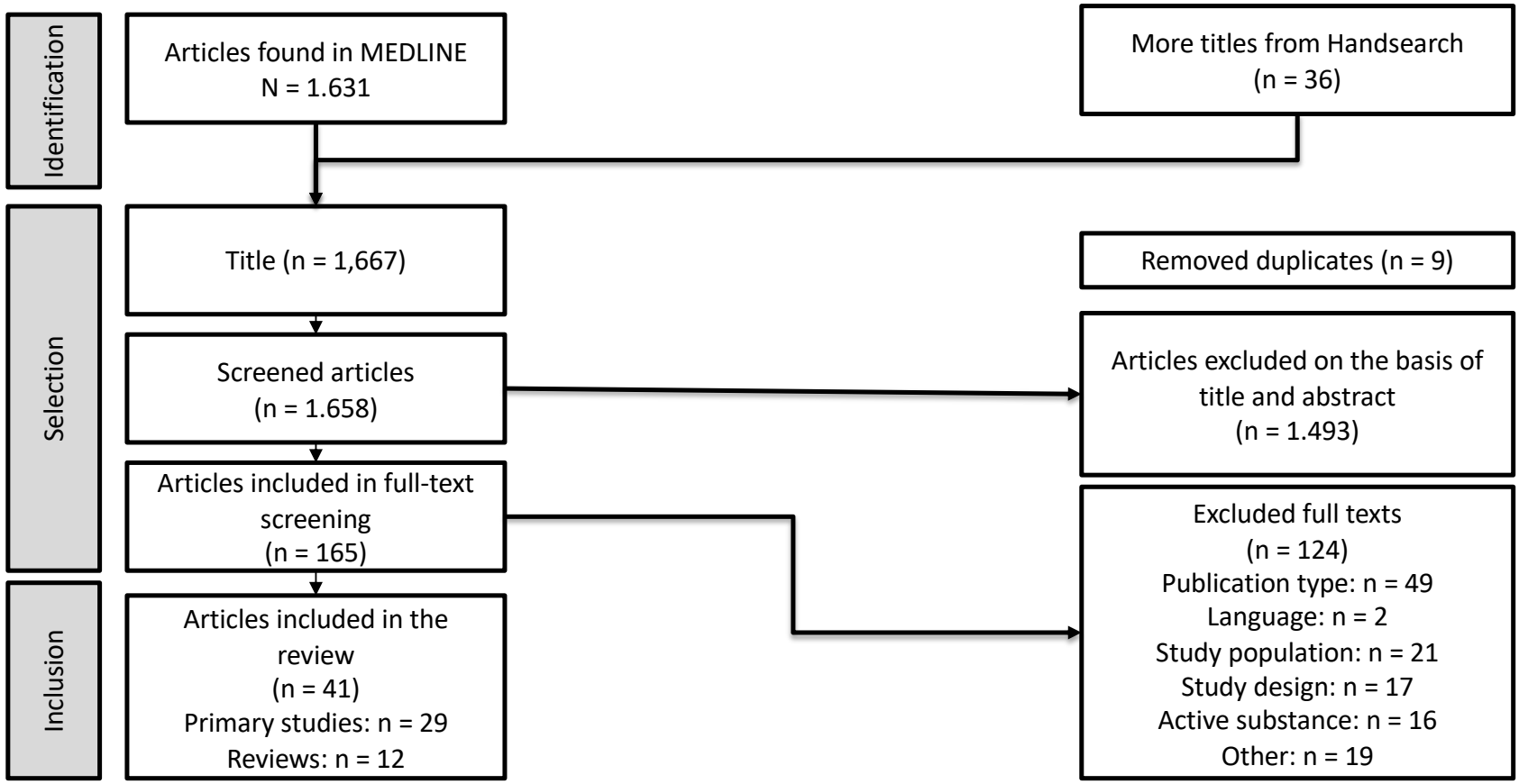
- ME / CFS, POTS
- little / no evidence: post-inflammatory ME / CFS
- little / no evidence: all causes

- Prevention of Long COVID / Post-COVID

Off-Label Use

Evidence Research

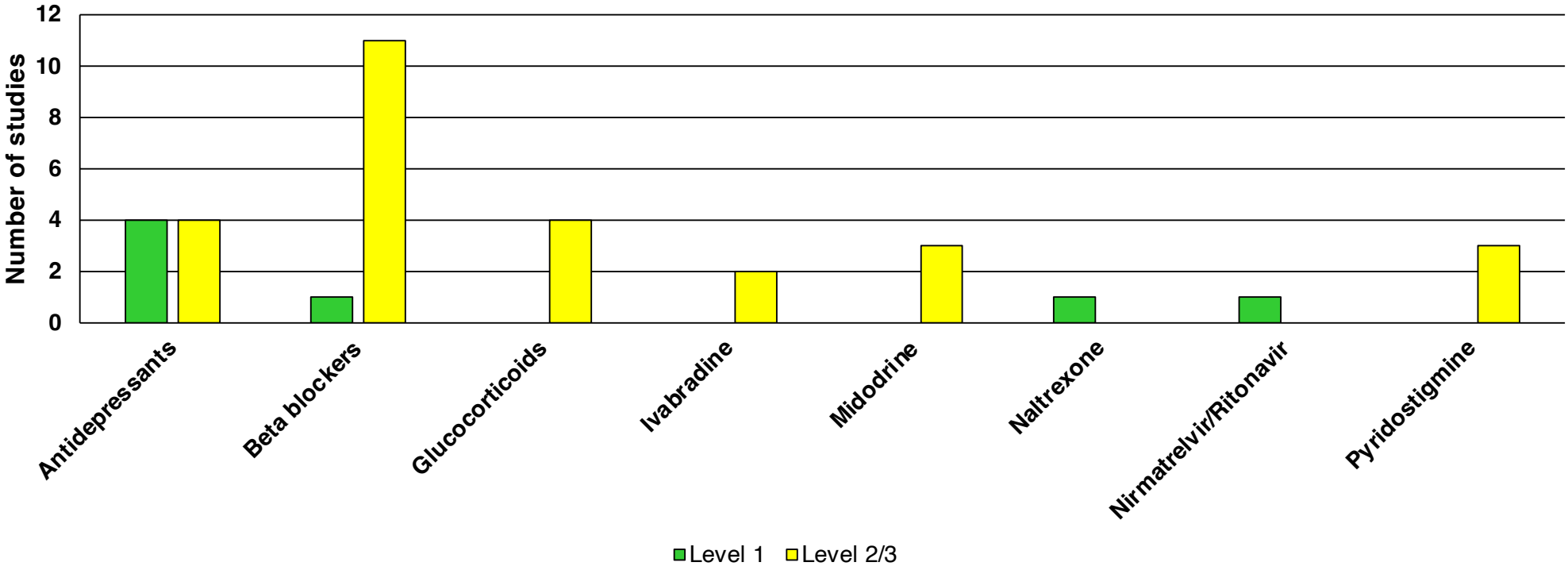
WIG 2



Off-Label Use

WIG 2

Evidence Research



No hits for statins, aripiprazole, metformin

Off-Label Use

Ivabradine

WIG 2

Abdelnabi et al. (2023)

Pre-post cohort study

n=55 adults with COVID-19 associated POTS

Intervention: 1 week

- 5 mg ivabradine twice daily

Outcomes

- Heart rate
- Heart rate variability
- Symptoms of POTS

Adverse events

- Not specified

Heart rate

- Significant reduction in average HR (p=0.001) and minimum and maximum HR (p<0.0001)

Heart rate variability

- Significant increase in SDNN and rMSSD HRV (p<0.0001)
- Low frequency/high frequency: not significant

Table 3. Comparison between heart rate and heart rate variability parameters before and after ivabradine therapy

Heart rate and heart rate variability parameters (N = 55)			
	Before Ivabradine	After Ivabradine	*P*-value
HR data			
Average HR (24 H) (bpm)	82.2±11.2	75.1±11	0.001*
Min. HR (24 H) (bpm)	63.5±5.8	58.4±5.1	< 0.0001*
Max. HR (24 H) (bpm)	146.9±15.3	118.7±18.1	< 0.0001*
HRV data			
SDNN (ms)	123±21.6	177.6±45.1	< 0.0001*
rMSSD (ms)	100.4±19.4	157.2±34.6	< 0.0001*
LF (ms^2)	633.1±197.7	656.8±181.1	0.51
HF (ms^2)	1848±229.1	1881.4±225.1	0.44

Results are represented as numbers (%) or mean ± standard deviation, BPM: Beats per minute, HR: Heart rate, HRV: Heart rate variability, LF: Low frequency, HF: High frequency. *P value ≤ 0.05.

Symptoms

- n=43 (78%) reported an improvement in symptoms (episodes of palpitations)

Off-Label Use

Ivabradine

WIG 2

Taub et al. (2021)

Cross-over RCT

n=22 adults with POTS

Intervention: 4 weeks ivabradine

- IG: 5 mg ivabradine twice daily (reduce or increase the dose to 2.5 mg)
- KG: Placebo

Primary Outcome

- Heart rate

Secondary Outcome

- Quality of Life (SF-36)

Explorative outcome

- Norepinephrine plasma levels

Adverse events

- Not going beyond side effects

Heart rate (IG vs. KG)

- Significant reduction in heart rate when standing (p=0.001) and lying down (p=0.001)
- Significant attenuation of the heart rate lying → standing (p=0.001)

TABLE 2 The Effect of Ivabradine on Heart Rate

	Baseline	Ivabradine	Placebo	p Value	Cohen's D	95% CI
Supine heart rate, beats/min	73.6 ± 11.7	64.9 ± 6.5	77.5 ± 12.8	0.001*	1.26	0.706-1.820
Standing heart rate, beats/min	95.1 ± 16.8	77.9 ± 9.3	94.2 ± 16.2	0.001*	1.05	0.544-1.58
Delta heart rate (standing vs. supine), beats/min	21.4 ± 15.3	13.1 ± 8.6	17.0 ± 10.4	0.001*	0.753	0.300-1.250

Ivabradine significantly lowers heart rate compared with placebo ($p < 0.001$). Ivabradine also significantly decreases the surge in heart rate upon standing ($p = 0.001$) compared with baseline with a 2-way interaction of treatment and body position. Parameters reported as mean ± SD. p-values compared mean parameters between placebo and ivabradine. $n = 22$. *Statistically significant ($p < 0.05$).

CI = confidence interval.

Quality of Life (IG vs. KG)

- Physical functioning: p=0.008
- Social functioning: p=0.021
- Other subscales: not significant

Norepinephrine plasma levels

- Not significant

Off-Label Use

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Off-Label Use

Vortioxetine

WIG 2

McIntyre et al. (2024)

RCT

IG: n=73-75, KG: n=74

Adults with post-COVID

Badulescu et al. (2024), Le et al. (2024), Kwan et al. (2024)

Intervention: 8 weeks of vortioxetine

IG: 5 - 20 mg/day (increasing the dose)

CG: Placebo

Primary Outcome

Cognitive function (DSST)

Secondary Outcome

Depressive symptoms (QIDS-SR-16)

Health-related quality of life (WHO-5)

Cognitive function (intervention vs. placebo after 8 weeks)

adjusted for sociodemographic variables, depressive symptoms and baseline scores

Significant difference: p=0.028

Depressive symptoms (intervention vs. placebo after 8 weeks)

Significant difference: p=0.026

Health-related quality of life (intervention vs. placebo after 8 weeks)

Significant difference: p=0.004

Functional impairment (intervention vs. placebo after 8 weeks)

Significant difference in all three domains

Social (p=0.048), work (p=0.016), family (p=0.028)

Off-Label Use

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Off-Label Use

Agomelatine

WIG 2

Pardini et al., 2014

Cross-over RCT

n=62 patients with ME/CFS (stage 3)

Intervention: 12 weeks

- **IG1: 50 mg agomelatine once daily**
- **IG2: 10 mg retarded melatonin once daily**
- **Subsequently, both groups for 12 weeks Agomelatine**

Primary Outcomes

- **Fatigue (Fatigue Severity Scale)**
- **Health-related quality of life (SF-36)**
- **Severity of the disease (CGI-S)**

Secondary Outcomes

- **Depression/anxiety (HADS)**
- **Daytime sleepiness (Epworth Sleepiness Scale)**

After 12 weeks

- **Significant interaction effect between group and time in favor of treatment with agomelatine**
  - **Fatigue ($p<0.001$)**
  - **Health-related quality of life ($p<0.001$)**
  - **Severity of the disease ($p<0.001$)**

After switching from melatonin to agomelatine

- **Reduction of fatigue ($p<0.001$)**
- **Increase in health-related quality of life ($p<0.001$)**
- **Reduction in the severity of the disease ($p<0.001$)**

Side effects/SUE

- **No differences between treatment groups**
- **Change from melatonin to agomelatine is not associated with side effects**

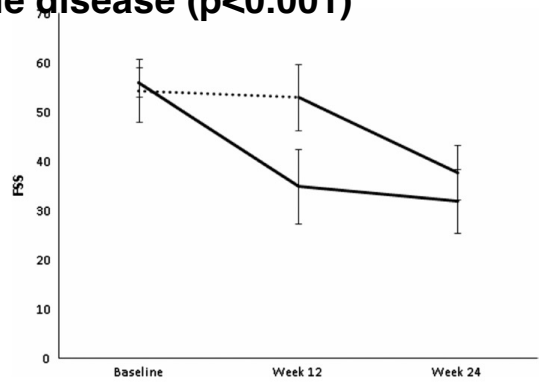

Figure 1 FSS score changes. Solid line represent agomelatine treatment, while dotted line represent melatonin treatment

Off-Label Use

Agomelatine

WIG 2

Medvedev et al., 2024

- Prospective observational study
- n=103 patients with depression within three months of SARS-CoV-2 infection
- Intervention: 8 weeks
  - 25 mg/day agomelatine
  - Increase to 50 mg/day if necessary
- Primary Outcome
  - Depression (Hamilton Rating Scale for Depression)
- Secondary Outcomes
  - Anxiety (Hamilton Rating Scale for Depression)
    - Item 10: "anxiety psychic" score
    - Item 11: "anxiety somatic" score
  - Severity of the disease (CGI-S)
  - Quality of life (SF-36)

- After 8 weeks
- Significant reduction in depression, anxiety and severity of illness ($p<0.0001$)
- 71.6 % of patients achieved remission of depression
- 81.4 % of patients: Reduction of the HADS score by 50
- Increase in quality of life ($p<0.0001$)

- Side effects/SUE
  - No adverse events due to treatment with agomelatine

Off-Label Use

Agomelatine

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Pardini et al., 2014

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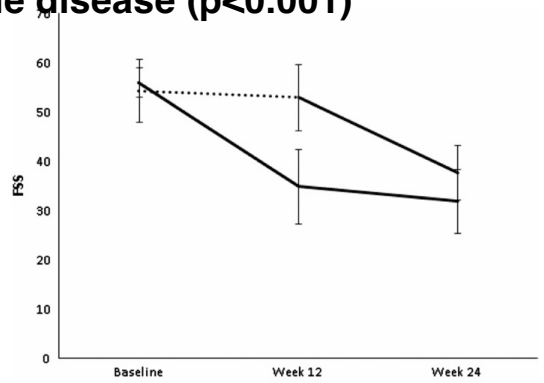

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Off-Label Use

Low Dose Naltrexone

WIG 2

O'Kelly et al. (2022)

Pre-post cohort study

n=38 adults with long COVID

Intervention: 2-3 months Naltrexone

- **Low dosage**
- **1st month: 1 mg/day; 2nd month: 2 mg/day; 3rd month: 3 mg/day**

Outcome

- **Questionnaire with seven domains**
  - **Perceived recovery from COVID-19, restrictions in every day activities, energy level, mood, pain, concentration, sleep**
- **Long COVID symptoms**

Adverse events

Table 2
Questionnaires at baseline and 2 month follow up.

Likert scale	Baseline questionnaire median(IQR)	2 month follow up median(IQR)	P value (2 tailed <0.05)
	N = 36	N = 36	
I feel I have recovered from COVID-19 (1–5)	1.5(1–2)	2(2–4)	**<0.001**
Does you health now limit you in you in daily activities? How much (1–3)	1(1–2)	2(1–2)	**0.001**
In the past 4 weeks do you have a lot of energy? (1–6)	3(2–3)	3(3–4)	**0.001**
In the past 4 weeks rate your overall mood(1–5)	2(2–3)	3(2–3)	.054
In the past 4 weeks rate you pain/discomfort (1–5)	2(2–3)	4(3–4)	**<0.001**
In the past 4 weeks rate your level of concentration(1–5)	2(1–2)	2(2–3)	**0.001**
Have you trouble staying or falling asleep(1–4)	2(1–3)	3(1–3)	**<0.001**

Long Covid symptoms: significant improvement of

- **Chest pain/tightness (p=0.047)**
- **Cough (p=0.016)**
- **Joint pain (p=0.008)**
- **Dejection (p=0.003)**
- **Change in character (p=0.001)**

Off-Label Use

Low Dose Naltrexone

WIG 2

Naik H et al.; 2024

Trial registration number: NCT05430152

RCT
N=160 (IG: n=80 / KG: n=80)

Intervention: 12 weeks LDN/placebo

Primary Outcome
- **Fatigue**

Secondary Outcome
- **Pain**
- **Severity of the symptoms**
- **Activity**
- **Quality of Life**

Further exploratory outcomes

Off-Label Use

Low Dose Naltrexone

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Secondary Outcome
- **Pain**
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- **Quality of Life**

Further exploratory outcomes

Off-Label Use

Low Dose Metformin

WIG 2

- Bramante et al. (2023) → LoE 1
- RCT (2 × 3 factorial design)
- Study population (1st group)
  - IG: n=663
  - KG: n=660
- Intervention: 14 days of metformin
  - Day 1: 500mg once a day
  - Day 2-5: 500 mg twice daily
  - Day 6-14: 500 mg in the morning, 1000 mg in the evening
- Long-term secondary outcome
  - Development of Long COVID (10-months follow-up)
- No adverse events
  - No differences in side effects between treatment groups

- Cumulative incidence after 300 days
  - Metformin: 6.3 %
  - Placebo: 10.4 %
  - Hazard ratio: 0.59 (95 % CI: 0.39-0.89; p=0.012)
- Greater effect with early start of treatment
  - Treatment with metformin within three days of symptom onset: HR: 0.37 (95% CI 0.15-0.95)
  - Start of treatment after four days or more: HR: 0.64 (95 % CI 0.40-1.03)

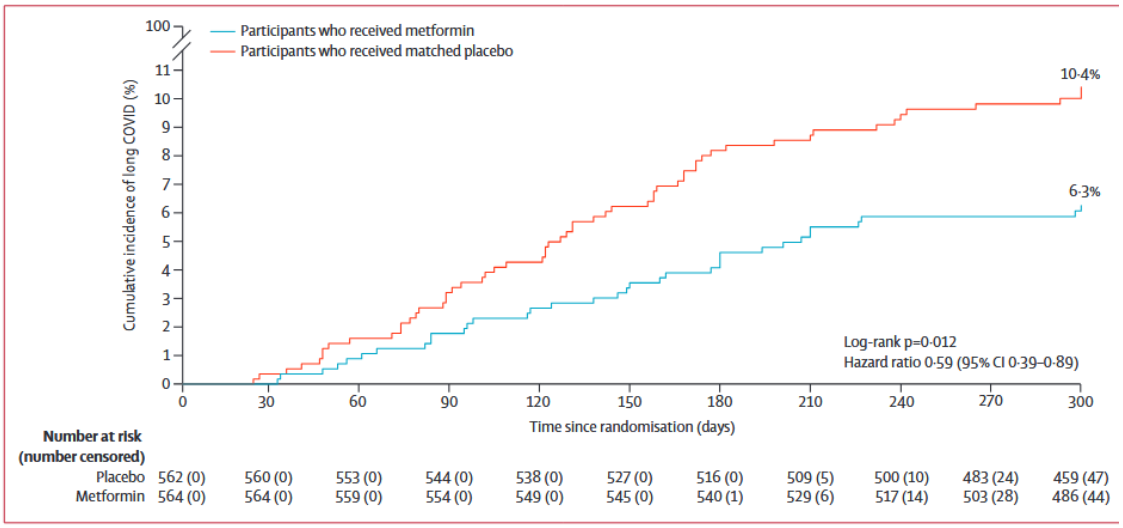

Figure 2: **Cumulative incidence of post-COVID-19 condition (long COVID) diagnoses over 10 months after randomisation**
The absolute risk reduction for metformin compared with matched placebo was 4·1% (95% CI 0·9–7·4).

Off-Label Use

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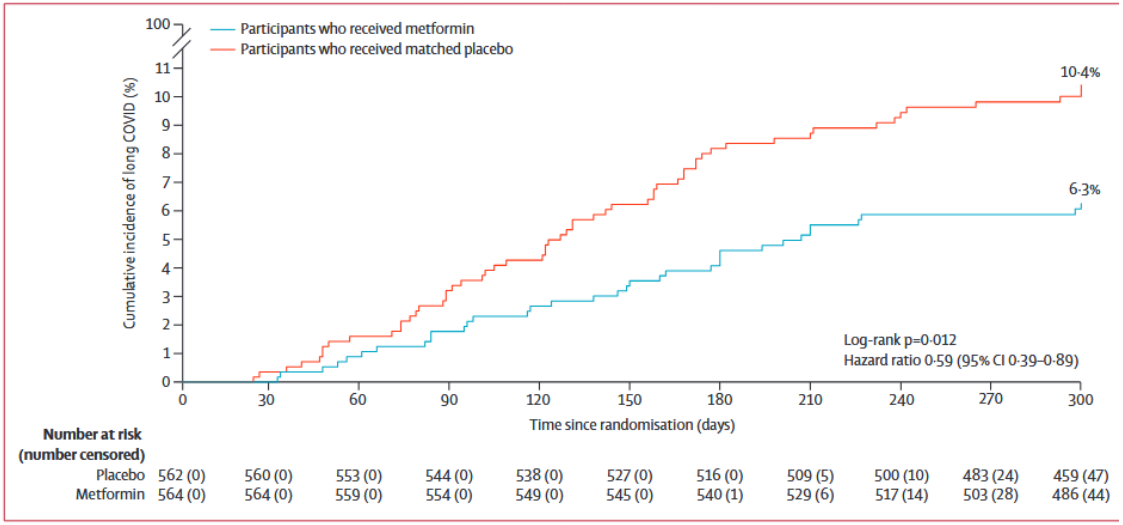
  - Start of treatment after four days or more: HR: 0.64 (95 % CI 0.40-1.03)



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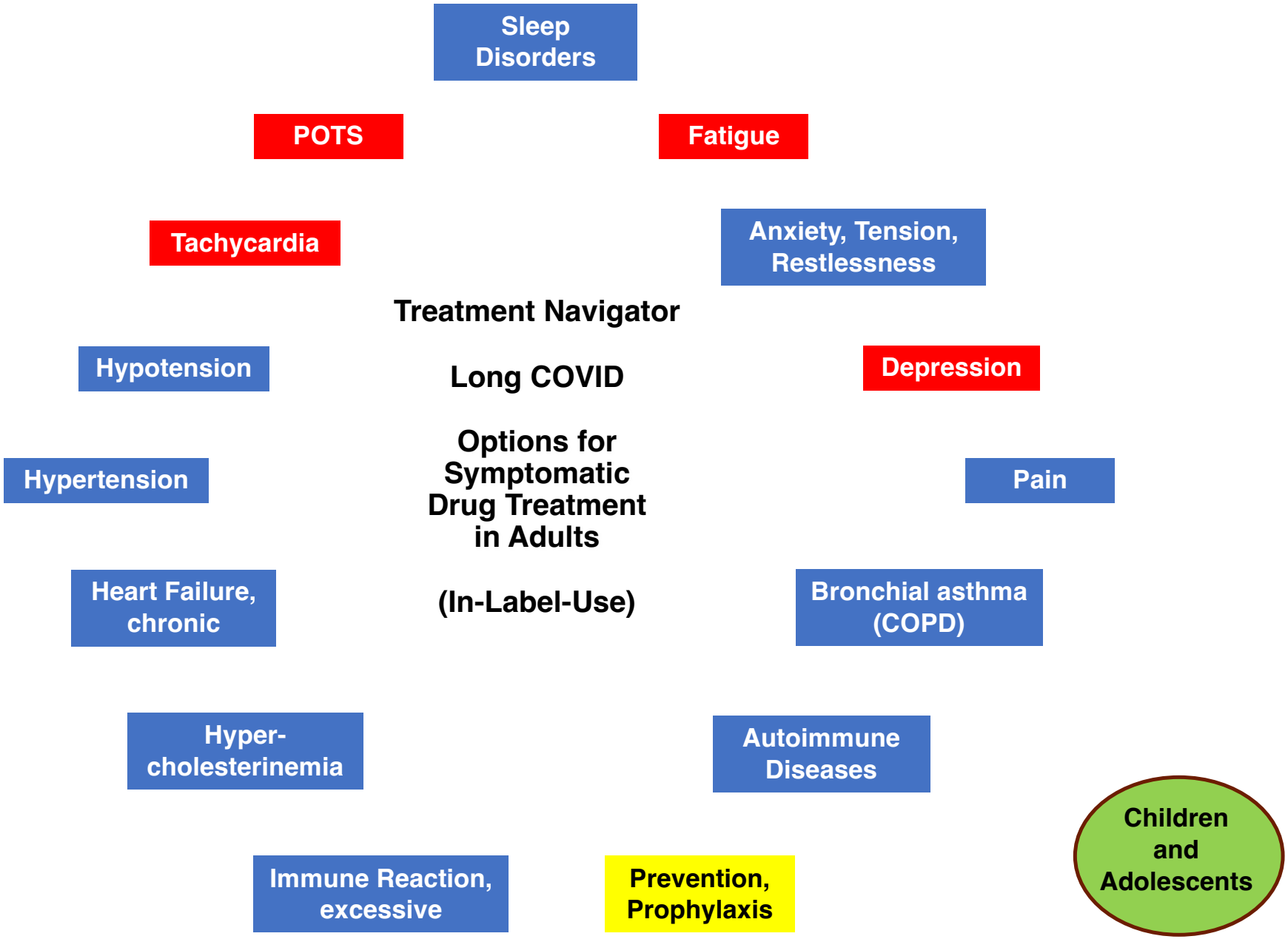
Sleep Disorders
POTS
Fatigue
Tachycardia
Anxiety, Tension, Restlessness
Treatment Navigator
Long COVID
Options for Symptomatic Drug Treatment in Adults
(In-Label-Use)
Hypotension
Depression
Hypertension
Pain
Heart Failure, chronic
Bronchial asthma (COPD)
Hyper-cholesterinemia
Autoimmune Diseases
Immune Reaction, excessive
Prevention, Prophylaxis
Children and Adolescents