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ORIGINAL ARTICLE

Opioid prescriber responsibility: A Danish drug utilization study

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Aims: We describe the distribution of prescribers responsible for opioid initiation and maintenance (general practice, hospital prescribers and other prescribers) in Denmark.

Methods: We leveraged data on opioid fills from a 20% sample of all Danes alive during 2000–2021.

Results: Overall, general practitioners were responsible for most treatment initiation (74% during 2000–2021) and maintenance treatment (92%). However, while hospital prescribers initiated ≈20% of treatments during 2001–2012, this increased to 35% in 2021. Similarly, hospital prescriber's share of maintenance treatment increased from 5.9% during 2000–2012 to 13% in 2021. This change was particularly pronounced for morphine initiation (48% hospital prescribers in 2021 up from 38% during 2000–2010) and oxycodone initiation (78% up from 41%). Regarding choice of opioids, codeine use dropped markedly, in particular among hospital prescribers. Tramadol was consistently the most common first choice opioid in general practice (33% in 2021), whereas its use among hospital prescribers decreased (54% during 2000–2015 to 15% in 2021). Conversely, the proportion of treatment initiation by hospital prescribers composed of morphine and oxycodone increased to 38% and 42% in 2021, respectively.

Conclusions: General practice prescribes most opioids; however, hospital prescribers are increasingly responsible for opioid prescribing, in particular initiation of morphine and oxycodone.

KEYWORDS
drug utilization, morphine and oxycodone, opioids, pain, pharmacotherapy, prescribing, tramadol

1 | INTRODUCTION

New guidelines and regulatory actions are continuously being developed to facilitate rational use of drugs. However, for such interventions to become most effective, it is essential to have both updated and detailed data on the use of drugs, including which physicians are responsible for issuing prescriptions for the drugs in question. The use of opioids has decreased markedly in Denmark from 2015 to 2019, primarily due to a decrease in the use of tramadol,[1] probably as a consequence of increased public awareness and

The authors confirm that the PI for this paper is Anton Pottegård.

regulatory risk minimization measures, which commenced during 2017 and 2018. Such changes are also likely to influence other aspects of opioid use, for example, which sector is responsible for prescribing these medications, and further are likely to affect physicians differently according to the sector they work in. To support further activities in promoting the rational use of opioids, we therefore aimed to describe changes in prescribers' responsibility for opioid initiation and maintenance in Denmark.

What is already known about this subject

- The use of opioids is debated, and most countries are implementing initiatives to restrict or even reduce their use.
- An understanding of which prescribers, for example, hospital physicians and general practitioners, that issue opioid prescriptions are important to target interventions on optimal opioid prescribing.

What this study adds

- General practitioners both initiate and maintain most opioid use in Denmark; however, hospital physicians are increasingly responsible for opioid prescribing.
- Hospital physicians and general practitioners use different opioids, with hospital physicians more commonly initiating oxycodone, in particular, but also morphine treatment.

2 | METHODS

2.1 | Data sources

For the main analyses, we identified a random 20% sample of all Danes alive at any point between 1 January 2000 and 31 December 2021.[2] Data on filled prescriptions (1995–2021) were obtained from the Danish National Prescription Registry,[3] containing data on all prescription drugs dispensed at community pharmacies to Danish citizens since 1995. The registry thus covers prescriptions issued both by hospital and primary care prescribers while in-hospital use of medicines is not covered. During the study period, such in-hospital use of opioids consistently comprised ≈4% of all opioids used in Denmark.[4] Drugs were categorized according to the Anatomical Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the World Health Organization (WHO).[5] Drug volume was expressed in defined daily doses (DDD), a technical unit of measurement defined by the WHO as "the assumed average maintenance dose per day for a drug used for its main indication in adults".[5] The Prescription Registry contains an identifier for the prescriber issuing the given prescription. The validity of the prescriber information in the Prescription registry has been found to be high and increasing over time.[6] As described previously,[2] we identified primary care prescribers via linkage to the Registry of Health Care Providers[7] while hospital physicians were identified based on falling within a distinct range of prescriber IDs. Based on this, we categorized prescribers into hospital prescribers, general practitioners (including out-of-hours practitioners) and other prescribers. For the supplementary analyses of regional variation, we used a different dataset covering all Danes receiving an opioid prescription 2014–2021.[1]

2.2 | Opioids

We identified all prescriptions for opioids, defined by ATC code N02A* (opioids) and R05DA04 (codeine). Opioids were grouped into morphine (ATC code, N02AA01), oxycodone (N02AA05 and N02AA55), transdermal opioids (N02AB03 and N02AE01), tramadol (N02AX02) and codeine (R05DA04, N02AJ06 and N02AJ07). These opioids covered 98.5% of all opioids prescribed in Denmark in 2021.[4] We defined *new use* of opioids as prescriptions marking the first opioid filled by the individual using a wash-out period of 5 years. All other prescriptions were classified as continued use. As an example, 2 prescriptions filled by the same individual for first tramadol and a year later oxycodone were thus classified as new use of tramadol and continued use of oxycodone. New use was defined across all opioids as to avoid classifying switching from, for example, tramadol to oxycodone as new opioid use. ATC codes and DDDs for opioids were based on the 2021 ATC/DDD index from WHO.[5]

2.3 | Analysis

First, the overall distribution of prescriber types responsible for opioid prescriptions was described annually from 2000 to 2021, dividing prescriptions into those representing new and continued use, respectively. This was done overall (i.e., for all opioids combined) and for the individual opioids. Second, we described changes in the distribution of single opioids issued by general practitioners and hospital prescribers, respectively, still dividing prescriptions into those representing new and continued use. Third, we described changes over time (2000–2021) in the mean and median number of DDDs for prescriptions representing new use, stratifying by individual opioids and by general practitioners and hospital prescribers. Finally, we repeated the first 2 analyses stratified by the 5 Danish regions and restricted to 2014–2021. Analyses were performed using Stata Release 17.0 (StataCorp, College Station, TX, USA).

2.4 | Ethics and regulatory aspects

According to Danish law, studies based solely on register data do not require approval from an ethics review board.[8] In terms of data protection, the study was registered at the repository of the University of Southern Denmark (10.825 and 10.490).

3 | RESULTS

General practitioners were responsible for most opioid prescriptions, issuing 74% of all prescriptions marking new use and 92% of prescriptions representing continued use over the entire study period. Corresponding numbers for hospital prescribers were 23 and 7.4% and for private practicing specialists 3.5 and 0.7%. However, there were considerable changes over time (Figure 1): the proportion of new treatment initiated by hospital prescribers was stable at around 20% from 2001 until 2012, after which it increased gradually to 35% in 2021, with a corresponding decrease in the proportion of prescriptions issued by general practitioners. A similar trend was seen for continued use, of which hospital prescribers were responsible for on average 5.9% during 2000–2012, increasing to 13% in 2021.

Changes in prescriber patterns for treatment initiation were seen for most individual opioids (Figure 2). For morphine, hospital prescribers were responsible for 48% of all first-time morphine prescriptions in 2021, an increase from on average 38% during 2000–2010. For oxycodone, 78% of new use were prescribed by hospital prescribers in 2021, up from an average of 41% during 2000–2010. For tramadol, corresponding proportions were 20% (2021) and 19% (2000–2010). Changes in responsibility for continued use were generally similar although less pronounced.

The distribution of opioids prescribed by both general practitioners and hospital prescribers changed markedly over time (Figure 3). In 2000, codeine comprised about half of all new prescribing (41% among hospital prescribers; 47% among general practitioners), declining to 3.2% for hospital prescribers and 34% for general practitioners in 2021. Tramadol was consistently the most common first choice opioid in general practice (33% in 2021), whereas its share of new hospital prescriptions decreased markedly from on average 54% during 2000–2015 down to 15% in 2021. Conversely, the proportion of new hospital prescriptions comprised of morphine and oxycodone increased to 41 and 40% in 2021, respectively. For continued use, both morphine and oxycodone prescriptions comprised increasing proportions of prescriptions among both general practitioners and hospital prescribers during the study period.

The mean and median DDD per prescription for new treatments (Table S1) increased for codeine among both hospital prescribers and general practitioners while it decreased considerably for transdermal opioids (from mean 41 DDD/prescription in 2000 to 17 in 2021 for general practitioners and from 22 to 16 for hospital prescribers). Conversely, the mean DDD per new prescription was stable for morphine and increased for oxycodone and tramadol for general practitioners, whereas it decreased during the study period for hospital prescribers from levels equal to or above those seen among general practitioners to levels below those for general practitioners.

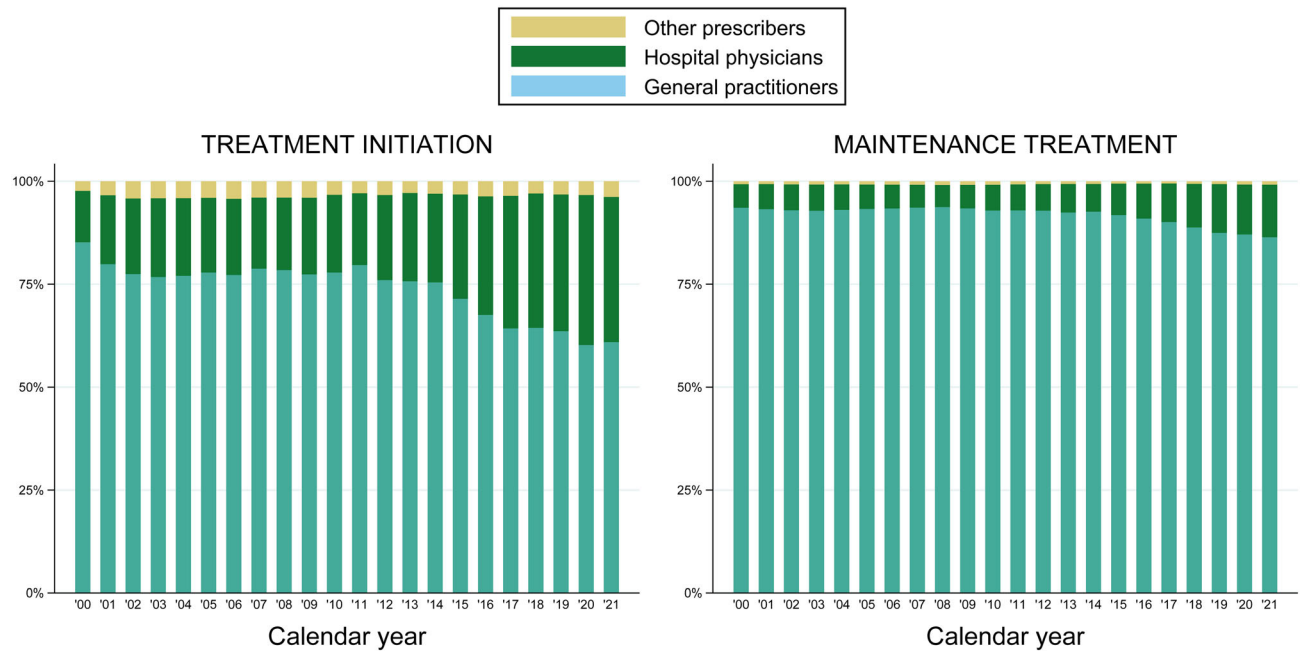

FIGURE 1 Proportion of opioids (any) prescribed by general practitioners, hospital physicians and other prescribers in Denmark during 2000–2021, and specified by whether a given prescription marked treatment initiation (first opioid in at least 5 years for that individual) or maintenance treatment (all other prescriptions).

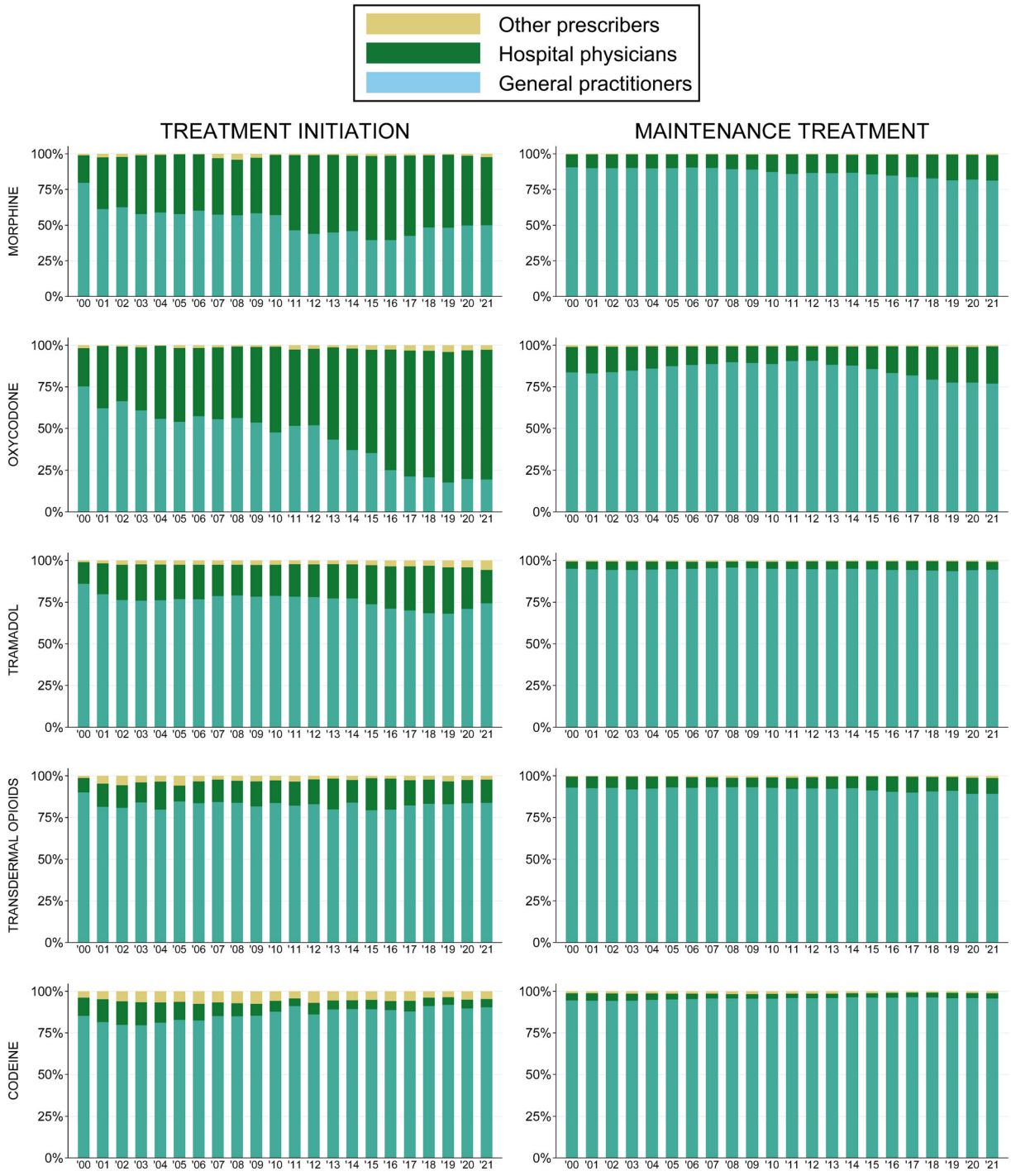

FIGURE 2 Proportion of individual opioids prescribed by general practitioners, hospital physicians and other prescribers in Denmark during 2000–2021, and specified by whether a given prescription marked treatment initiation (first opioid in at least 5 years for that individual) or maintenance treatment (all other prescriptions). Transdermal opioids include buprenorphine and fentanyl.

When stratifying by the 5 individual Danish regions (Figure S1), only small variance was found with a slightly higher proportion of hospital prescribers in the Region of Northern Denmark, a slightly lower proportion of hospital prescribers in the Region of Southern Denmark, and the remaining regions aligned with the country average.

4 | DISCUSSION

We describe how general practice has been and remains the sector prescribing most opioids in Denmark, but also how hospital prescribers are increasingly responsible for opioid prescribing, in particular initiation of treatment with oxycodone and morphine.

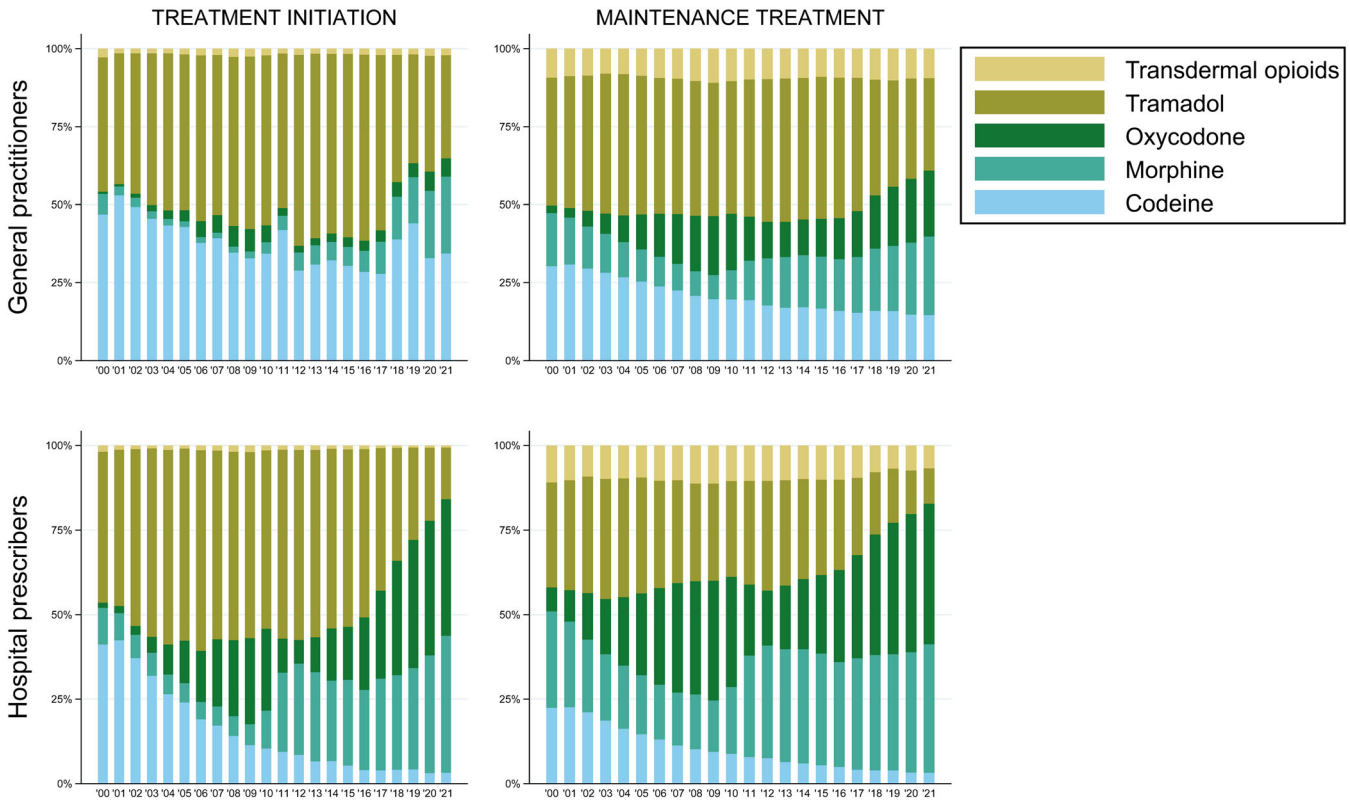

FIGURE 3 Distribution of types of opioids prescribed by general practitioners and hospital physicians in Denmark during 2000–2021 and specified by whether a given prescription marked treatment initiation (first opioid in at least 5 years for that individual) or maintenance treatment (all other prescriptions). Transdermal opioids include buprenorphine and fentanyl

The main strength of the study is the nationwide capture of high-quality prescription fill data[3] with long historical coverage and validated information on prescriber types.[6] Further, the use of data on filled prescriptions instead of issued prescriptions ensures that the reported use patterns are closer to actual opioid consumption with no influence from issued prescriptions that are never filled by the patient.[9] The main weakness of the study is the potential limited generalizability of the study findings outside Denmark, as the overall prescribing traditions are heavily dependent on the structure of the Danish health care system, and as the recent changes in opioid utilization are likely to be associated to the specific regulatory actions taken in 2017 and 2018.[1] Further, we could only provide overall utilization patterns as we were unable to break down prescribing by, for example, individual medical specialties.

We document that hospital prescribers are increasingly initiating treatment. However, it is an important contextualizing finding that the mean prescribed amount for opioid prescriptions marking treatment initiation has dropped considerably for hospital prescribers during the study period. This either reflects lower prescribed daily doses or shorter treatment durations or coverage of initial prescriptions or a combination hereof. This suggests that guidelines are increasingly followed and aligns well with our previous study finding that while the total number of opioid users increased slightly in recent years, the total opioid consumption decreased during the same period.[1]

To what extent changes in the distribution of prescribers responsible for opioid prescribing is linked to both media attention and regulatory actions such as, for example, those initiated in 2017–2018 is unknown. These regulatory changes included both temporarily raised requirements for reporting of adverse events to tramadol and permanent stricter prescription requirements for tramadol and codeine, for example, prohibiting repeat prescriptions allowing multiple dispensings.[1] Our findings generally show that these changes have happened gradually over the last decade among hospital prescribers, while there seems to be a more direct link to the decreasing proportion of tramadol initiation among general practitioners. Our findings also clearly document that opioid prescribing in Denmark changes dramatically over time and with an apparent acceleration of these changes towards the end of the study period. The most recent guideline in Denmark (issued in 2019)[10] emphasizes morphine as first-line opioid over oxycodone, tramadol and other opioids although opioid use is generally discouraged for chronic pain. This aligns well with current prescribing patterns among general practitioners but less so with those seen among hospital physicians. Our study findings thus suggest that future regulatory action and guidelines should increasingly, albeit not exclusively, focus on hospital prescribers who are increasingly responsible for opioid prescribing.

In conclusion, we provide detailed data on prescriber types responsible for opioid prescription in Denmark during 2000–2021.

These data will be useful to support future initiatives to further ensure the rational use of opioid analgesics by documenting several recent changes to prescribing patterns that needs to be considered, in particular an increasing proportion of opioid prescriptions being issued by hospital prescribers.

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COMPETING INTERESTS

The authors report no conflicts of interest relevant to the study.

AUTHOR CONTRIBUTIONS

Anton Pottegård, Lotte Rasmussen and Anne Mette Skov Sørensen framed the study question and all authors contributed to designing the study and the analytical protocol. Anton Pottegård and Morten Olesen completed all analyses. Anton Pottegård wrote the first draft of the manuscript, while all authors revised the manuscript and approved the final version for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Danish Health Data Authority. Restrictions apply to the availability of these data, which were used under license for this study. Data specifications and applications are available from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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