

OFP

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EDITOR'S MESSAGE

Distinctively a DO

RESEARCH ARTICLE

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Increase Efficiency and Osteopathic
Manipulative Treatment in a Family
Medicine Residency

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Identifying Symptoms and Triggers



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EDITOR'S MESSAGE

Distinctively a DO

Ronald Januchowski, DO, FACOFP, Editor, *Osteopathic Family Physician*

"What makes you different as a DO?"

I have heard that question numerous times over the past few decades from my patients, fellow physicians, relatives and the news media. It is a simple question but can be asked in many ways that can sometimes evoke emotional responses from the receiver. It seems that in the past, the osteopathic profession at times has supplied a message of how a DO is much the same as an MD, often to provide credentialing boards, hospital systems and insurance companies the basis to provide equal access to positions and payment parity for the work we do.

As an osteopathic family physician, I sometimes take for granted the unique nature of the DO degree and reinforce the similarities. I remember a study that I did while in a "dually-accredited" residency program that looked to see if DO students maintained their osteopathic identity while in an allopathic predominant teaching environment. One of the difficulties with the study was defining the "osteopathic identity." Students could clearly identify OMM as a physical difference for DO physicians; however, they had more problems defining some of the intangible ideas involved.

In the past month, I have had opportunities to dwell on the differences due to a couple of events. As the President of our state Osteopathic Medical Society, I created a news media presentation about the DO difference. The other event involves OFP applying for a nationally recognized publication identifier. Both events made me have to answer the question at the start of this message in a thoughtful manner that would make sense to everyone.

The osteopathic tenets, doing OMM in clinic and a review of Dr. A.T. Still's sayings made me wonder if there was an easy way to signal the audience's answer. I think that I, as much of our readership, realizes that the DO distinctiveness is a combination of many things and much as we do not limit our treatment of patients to just the disease, being a DO requires an assembly of mind, body and spirit. I hope that this issue of OFP demonstrates this incredible uniqueness that is so intrinsic to our profession.

Celebrate your DO distinctiveness this month and enjoy the OFP March/April 2021 issue! Share how you define your osteopathic identity. #DODifference

#DODIFFERENCE

FROM THE PRESIDENT'S DESK



Organizational Innovation: Meeting the Demands of Today's Osteopathic Family Physicians

Nicole Heath Bixler, DO, MBA, FACOFP

ACOFP President

What is innovation? At the core, it is a concept that refers to an individual or organization developing new ideas, enacting new processes or taking a different approach to an existing plan. It is not just a buzzword; it is a necessary component to remain relevant and successful. This has become even more important as technological advances in learning, medicine and business are an almost daily occurrence. Add a once-in-a-century global pandemic to the mix, and the need to innovate has become a survival mechanism.

So how is ACOFP rising to the challenge to remain true to its core values while innovating to meet the demands of today's osteopathic family physicians? By taking a deeper look at our educational products, our governance structure and our responsibility to promote health equity and social justice. Additionally, we have established our advocacy priorities to align with your needs as physicians practicing in an environment that is continually influenced by scientific and technological advancements.

When I worked with ACOFP staff and leaders to create the Task Force on Convention Innovation in December 2019, we had no idea that our need for innovation would be at the hands of a virus that precluded us from meeting in person in New Orleans in March 2020. One year later, our collective duty to the health and safety of our communities and families has brought us to our second virtual ACOFP Annual Convention and Scientific Seminars.

Educating in this completely virtual platform allows us the opportunity to expand our content and allows you the flexibility to learn at your convenience. During the convention, you can connect with your colleagues through virtual discussions and various networking tools, while hearing from our convention partners as they provide you with the latest in cost-effective solutions and products that will allow your practice and patients to thrive. These changes in our convention delivery may have been forced upon us, but we know there is no going back. We will continue to implement the recommendations of the task force by personalizing the attendee experience, diversifying our educational choices and examining how we will evolve into a hybrid educational meeting in the future.

As we continue to revolutionize our CME offerings, we must support those efforts with an effective governance structure and a clear mission. To that end, with the help of an external advisory group, we have completed the first assessment of our current governance structure compared to other healthcare organizations and industry leaders. Our next step involves collecting additional member feedback, completing a deeper-dive assessment and making recommendations for more inclusive and efficient governance, while maximizing our volunteer and staff resources

to advance the strategy of ACOFP. The goal of this work is to allow our organization to remain proactive, relevant and adaptable.

In tandem with our convention and governance task forces, there was a definitive need to establish the Task Force on Racism and Health to develop new plans to address existing disparities. Expanding upon the exploratory meetings of our three sub-committees, our next steps include developing a defined work plan to help family physicians play a role in ending health disparities due to racism and discrimination.

The very institution of osteopathic medicine is based on the holistic approach to a patient, which certainly includes understanding a patient's personal experiences with discriminatory behavior based on race, gender identity, sex, sexual orientation, religion, ethnicity, geography and socioeconomic. As physicians, we have an opportunity to lead the transformation and healing of our communities that have been devastated by inequality. This will only be possible if we continue to advocate for the value and innovative spirit that family physicians can provide to all patient populations.

ACOFP has determined the following as its healthcare system reform advocacy priorities for 2021:

- Protect patients from COVID-19
- Encourage appropriate use of telehealth
- Address the family physician shortage
- Reduce unnecessary paperwork requirements
- Improve outcomes and decrease costs through primary care and support of family physicians
- Preserve the family medicine model of care
- Focus on vulnerable populations and address racial disparities
- Address the opioid crisis

As an organization, we look forward to continued creativity and innovation in addressing the needs of our members and our patients. I am appreciative of the hard work and dedication of our committees, task forces, governors and staff who have made ACOFP successful in its endeavors thus far. As we continue our efforts, we will keep the words of American physicist William Pollard in mind: "Learning and innovation go hand-in-hand. The arrogance of success is to think that what you did yesterday will be sufficient for tomorrow." May we all be successful in our tomorrows.

Osteopathically,

Nicole Heath Bixler, DO, MBA, FACOFP

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Monica M. Woodall, DO, FACOFP
Amanda S. Wright, DO

Silver Level (\$2,500+)

Victor D. Angel, DO
Peter F. Bidey, DO, FACOFP
William J. Burke, DO, FACOFP
Robert P. Camara, DO
Tyler C. Cymet, DO, FACOFP
Robert J. George, DO, FACOFP *dist.*
Douglas W. Harley, DO, FACOFP

Nicklaus James Hess, DO
Ryan Huang, DO
Anne L. Hutchinson, DO
Ronald P. Januchowski, DO, FACOFP
Mark K. Kauffman, DO
Duane G. Koehler, DO, FACOFP *dist.*
Glenn K. Moran, DO, FACOFP
Terri Ann Nickel, DO, FACOFP

Gary L. Patzkowsky, DO, FACOFP
Sean P. Perrine, DO
George T. Sawabini, DO, FACOFP *dist.*
Christopher B. Scuderi, DO
Jay H. Shubrook, Jr., DO, FACOFP
George Thomas, DO, FACOFP
Rachel A. Young, DO
Thomas G. Zimmerman, DO, FACOFP

Bronze Level (\$1,000+)

Steven G. Bander, DO, FACOFP *dist.*
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Jeff Borchardt
Per Gunnar Brolinson, DO, FACOFP
Michael G. Burry, DO, FACOFP
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Traci-lyn Eisenberg, DO
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Nelson Eng, DO, FACOFP
Karen Frayser Evans, DO
Ian L. Fawks, DO, FACOFP
Michelle Fiorillo, DO
Jodi S. Flanders, DO, FACOFP
Ernest R. Gelb, DO, FACOFP
Joan M. Grzybowski, DO, FACOFP
Hilary S. Haack, DO

Gerald L. Haas, DO
Patrick J. Hanford, DO, FACOFP *dist.*
Patricia Eileen Happel, DO, FACOFP
Jennifer J. Hauler, DO
Charles E. Henley, DO, FACOFP
Kathleen M. Henley, DO
Sarah J. James, DO, FACOFP
Mark Jeffries, DO, FACOFP
Steven D. Kamajian, DO, FACOFP
Royce K. Keilers, DO, FACOFP *dist.*
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Ronna D. New, DO, FACOFP
Lorenzo L. Pence, DO, FACOFP
William J. Pettit, DO
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Bruce G. Rankin, DO, FACOFP
Bret D. Ripley, DO, FACOFP *dist.*
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Norman E. Vinn, DO, FACOFP
Alesia J. Wagner, DO, FACOFP *dist.*
Jacqueline Weaver-Agostoni, DO, FACOFP
Janette M. Willcox, DO, FACOFP
Margaret A. Wilson, DO

RESEARCH ARTICLE

USE OF LEAN MANAGEMENT TO INCREASE EFFICIENCY AND OSTEOPATHIC MANIPULATIVE TREATMENT IN A FAMILY MEDICINE RESIDENCY

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KEYWORDS:	ABSTRACT:
Family Medicine Residency	Objectives: To determine Lean management's ability to improve the efficiency of residents and increase osteopathic manipulative treatment (OMT) in a family medicine residency clinic.
Key Performance Indicator	Methods: A Key Performance Indicator Board (KPI), a process of Lean management, was created in a residency clinic by various staff. Patient wait times were chosen for the quality measure and daily huddles took place to track progress. A “5-why” was conducted to determine the reasons for failure to meet goals. Faculty used this information to create the 5 “S” of Efficiency method to help residents improve timeliness in caring for complicated patients. Comparisons of the number of patient visits failing wait time goals and total OMT performed before and after the intervention was analyzed. Chi-square was used for statistical analysis and the p-value was set at 0.05.
Lean Management	Results: Implementation of the 5 “S” of Efficiency method resulted in a significantly lower percentage of days failing the wait time goal in comparison to months before the intervention (p = 0.00001): the average percentage of failed days decreased from 43.1% to 10.4% with the intervention. Enacting Lean management also resulted in a significantly greater percentage of billed OMT billing codes (6.8% vs. 5.3%) (p = 0.03).
Osteopathic Manipulative Treatment	Conclusion: This study indicates that the use of Lean may reduce patient wait times and lead to increased OMT use among family medicine residents. Use of Lean or the 5 “S” of Efficiency method may help other osteopathic programs attempting to improve care; however, further research is indicated.
Patient Wait Time	

INTRODUCTION

Lean management (or Lean) is a thought process for team environments that analyzes current workflow processes to eliminate non-value-added activities and improve outcomes in areas of time, cost or safety. Though it began in the industrial field, Lean has been gradually applied to the health care sector, particularly in the hospital domain (such as in surgery or emergency departments).¹ Reviews support the trend of successful

Lean utilization within larger health care institutions that serve urban populations.^{2,3} One such large health care organization of a midwestern city described in this study has utilized Lean through the use of Key Performance Indicator (KPI) boards. These boards require all department areas to regularly meet to discuss goals (or performance indicators) while also tracking daily progress in improvement. Daily huddles around KPI measurements bring awareness to issues, track small improvements and foster a modality for continuous refinement. KPI boards have been implemented successfully across the system’s affiliated hospital units, but only recently have they been explored in its ambulatory settings.

Ambulatory clinics are amenable to the improvements in efficiency and productivity that Lean offers, but few studies exist. In one example, the University of Virginia Gynecologic Oncology clinic implemented Lean to significantly decrease total mean wait

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times from 119 minutes to 82 minutes.⁴ Review of the literature indicates even less exploration of Lean in ambulatory medical education residency clinics. The few studies available in Internal Medicine and Family Medicine Residency provide some insight into the benefits gained. Lean principles helped to significantly decrease patient wait times⁵ or improved patient volumes and satisfaction through a better workflow in these residency settings.⁶ Such time efficiency could be useful to a residency clinic where residents learn to optimize patient care and integrate osteopathic manipulative therapy (OMT) into visits.

In a family medicine residency clinic in central Ohio that has received accreditation from the Accreditation Council for Graduate Medical Education (ACGME) and osteopathic recognition (OR), efficiency has been an ongoing goal. The faculty teach residents that improved efficiency will increase patient satisfaction, performance on system-based scorecards and time availability to perform OMT. It has been reported that lack of time is the main reason physicians express failure to use OMT⁷ and similar reasoning has been expressed to faculty in this program. As an OR program, methods must be utilized to increase OMT opportunities through gained time efficiency. Residents balance the development of knowledge, time management skills, physician to patient dynamics and application of osteopathic principles regularly. As such, the faculty believed that the residents were amenable to the continuous feedback afforded by Lean to improve.

This project was a retrospective review of data on Lean management's effects on patient wait times and utilization of OMT over several months at a central Ohio family medicine residency clinic. This quality improvement study had the following specific aims:

AIM #1: Compare the percentage of average visits with prolonged wait times before and after implementing Lean techniques for time efficiency (the 5 "S" of Efficiency, as described in methods.)

AIM #2: Compile data regarding the reasons for each failed occurrence in meeting the wait time goal.

AIM #3: Compare the percentage of OMT in patient visits performed before and after the implementation of Lean.

Due to its reported successes in many areas important to patient care,^{1-6, 8} Lean management was hypothesized to help achieve decreased wait times and increased utilization of OMT in patient visits. It was also thought that data from this study could assist other osteopathic recognized family medicine residency clinics in improving efficiency and enhancing time organization for better patient care.

METHODS

We proposed a retrospective review of wait times and use of OMT from data obtained after the implementation of Key Performance Indicator (KPI) Board huddles in a family medicine residency. The data collected included all patient visits seen by both residents and attending physicians at the ambulatory clinic from August 2018 through May 2019. Only the days when physicians were working and seeing patients were included. An overview of the project parameters is found in Table 1.

TABLE 1:

Outline of parameters collected for the study.

CATEGORY	DATA POINTS
Wait time goal	Days when wait time goal was or was not met before implementation of Five-S of Efficiency method
Reasons for failed occurrences in meeting the wait time goal	<ol style="list-style-type: none"> 1. Doctor running behind 2. Unavailable staff 3. Complicated patient 4. Delay from testing
Proportion of OMT used	<ol style="list-style-type: none"> 1. Percentage of OMT used during appointments before and after implementation of 5 "S" of Efficiency method 2. Numbers of various OMT Current Procedural Terminology (CPT) codes billed before and after intervention

KEY PERFORMANCE INDICATORS (KPI)/LEAN INITIATION

The project utilized data compiled from KPI board huddles. A KPI board uses a visual tracking system that records processes and effects of Lean management on specific indices (chosen by a team) for five indicators: Safety (S), Quality (Q), Delivery (D), Productivity (P) and Cost (C). A data collection page was used to show whether or not goals were met and a living Pareto chart recorded the reasons why a goal was not achieved. A Pareto chart is a bar graph that lists reasons for a particular outcome and assumes a majority of problems stem from a common cause.

Resident efficiency was chosen for the KPI indicator of "Quality" (Q) shortly after the Lean process was initiated and patient wait time was selected as its index. Daily KPI board huddles, attended by faculty, residents and staff, allowed a modicum to discuss measures (such as the wait time goal), whether or not goals were met and reasons for any failure.

The initial goal for the Quality ("Q") indicator stated that patient wait times would be less than one hour from the time of rooming to the time the resident entered the exam room (Table 2). The medical assistants and front desk staff recorded the information related to wait time. However, in the spirit of Lean, continuous assessment led to the amendment of the wait time goal throughout the study period, as listed in Table 2.

TABLE 2:

Outline of the wait time goals throughout the study.

MONTH	GOAL
August 2018 – November 2018	Patient wait time < 1 hour from rooming to 1st resident doctor visit
December 2018 – January 2019	Patient wait time < 90 minutes from appointment time to checkout time
February 2019 – March 2019	< 3 patients wait 90+ minutes from appointment time to checkout time
April 2019 – May 2019	< 2 patients wait 90+ minutes from appointment time to checkout time

WAIT TIME GOALS

The wait time goal was amended based on the trend of results and the KPI board members' opinions. In February, due to better ease of tracking and attaining more valuable information, the revised goal was to have less than or equal to three patients daily fall outside a wait-time goal of 90 minutes. This change factored in care variables, such as additional testing, treatments, emergency services or other unforeseen circumstances outside resident control. In April, the goal was reduced to less than two patients for the entire day due to success with the intervention and idealization for even better outcomes.

Primary Intervention: The 5 “S” of Efficiency

The KPI huddle participants conducted a “5-why” process to help outline reasons for and steps leading to failure using a living Pareto chart. Over time, the Pareto identified that organizing complex patient problems during a visit was the most common reason misses occurred. Therefore, the faculty created the 5 “S” of Efficiency method, which was implemented at the start of October 2018 and ultimately acted as the study's primary KPI/Lean intervention. This 5-step method had the resident organize each appointment by doing the following (Table 3): 1) Start the visit, 2) Set the agenda, 3) Stick to the plan, 4) Succinctly summarize and 5) Serve the patients/staff well. Faculty taught the process to residents at didactic sessions, provided pocket cards to carry in white coats listing the 5 “S” of Efficiency method and reviewed it regularly during case discussions. The KPI board and daily huddles continued to track data after the installment of this intervention.

For the OMT portion of the study, a retrospective review of OMT data was obtained from the same time frame of August 2018 through May 2019 using Current Procedural Terminology (CPT) codes for OMT (98925-98929). A comparison of the percentage of OMT used before and after the initiation of the 5 “S” method was analyzed. We reviewed the total number of codes billed, as well as the complexity of the CPT codes in these periods. Higher CPT code levels denoted more body systems upon which OMT was used during a visit.

TABLE 3:

Explanation of the 5 “S” of Efficiency method.

1. Start the visit: a. Pre-chart (<i>working before the visit to prepare for the day</i>) b. Predict (<i>predicting what the patient's needs will be based on past progress note review, prescriptions needing refilled, etc.</i>) c. Prime the day (<i>huddling with a medical assistant on the day's schedule and starting the first patient on time</i>)
2. Set the agenda: (<i>organizing the visit at the beginning for better, more efficient use of time</i>)
3. Stick to the plan unless history or physical exam suggest otherwise: (<i>Following the agenda unless conditions warrant straying from it, using clinical resources, such as the behaviorist and pharmacist to help manage conditions and having standard methods to review problems, such as templates</i>)
4. Succinctly summarize: (<i>When presenting to the attending, omitting unnecessary detail</i>)
5. Serve the patients/staff well: (<i>Keeping in mind the importance of always addressing the patient's needs sufficiently, regardless of the time it takes</i>)

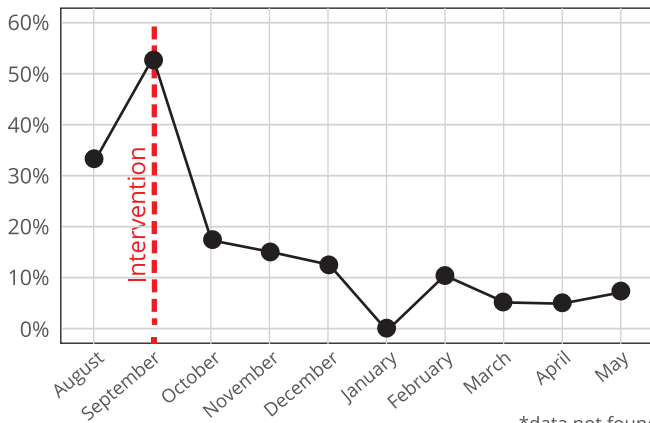
The data for this quality improvement project was accessible to only allow applicable investigators. The study's activities did not prevent or hinder the delivery of care to patients, nor did they impose greater than minimal risks or burdens on them. The potential loss of confidentiality was minimized by storing data on password-protected computers secured within the residency offices. Data usage followed the Health Information Privacy and Accountability Act (HIPAA) guidelines and only de-identifiable CPT codes were stored and analyzed. For descriptive statistical analysis, wait time goals and total OMT were reported using frequencies and percentages. The comparison of pre-intervention and post-intervention data was performed using the chi-square test. The p-value for the significance for these was set at 0.05.

RESULTS

The months after Lean management initiation revealed a significantly lower percentage of days failing the wait time goal in comparison to months before the intervention ($X^2 = 19.95, p = 0.00001$). A trend of the percentage of days each month with failed wait time goal is shown in Figure 1. The average percentage of failed days decreased from 43.1% to 10.4% with the intervention. The trend line demonstrates how the application of Lean management in October 2018 immediately led to a sharp decrease in the percentage of failures. Subsequent months of Lean management showed a continued declination of the failure rate.

FIGURE 1:

The percentage of days each month with failed patient visit wait time goal.



The graph illustrates changes before and after the initiation of Lean management. The red line denotes the timing of intervention (implementation of the “5-s” of Efficiency method).

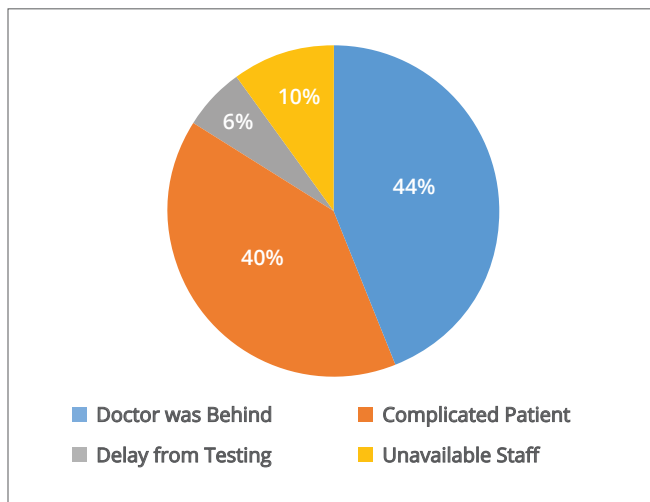
*Indicates missing data for January (statistical analyses did not include this month).

Reasons for Failing Wait Time Goals

As indicated in Figure 2, the most common reasons reported for failed wait time goals were doctor/medical student behind (44%) and complicated patient (40%), while less common reasons were unavailable staff (10%) and delay from testing (6%).

FIGURE 2:

Reported reasons for not meeting patient visit wait time goal. N = 68.



Proportion of OMT Used

Enacting Lean management from October 18 to May 19 resulted in a significantly greater percentage of billed OMT CPT codes (6.8% vs 5.3%), ($X^2 = 4.53, p = 0.03$). Table 4 displays the effect Lean management had on the proportion of OMT CPT codes billed by physicians in the clinic. The percentage of the variety of codes used did not significantly differ ($X^2 = 3.00, p = 0.39$). Table 5 demonstrates the comparison of different levels of OMT CPT Codes billed before and after initiation of Lean management. The enactment of Lean management did show a trend of the increasing percentage of higher-level OMT codes billed, though not statistically significant (6% vs. 2% and 0.2% vs. 0% for the CPT codes of 5–6 body regions and 7–8 body regions, respectively).

TABLE 4:

Summary of the proportion of different OMT CPT codes used before and after enacting Lean management.

TIME PERIOD	COUNT OF TOTAL VISIT CPT CODES	COUNT OF OMT CPT CODES	% OMT BILLED
August 18 to September 18	1,552	83	5.3%
October 18 to May 19	6,347	434	6.8%

TABLE 5:

Summary of the proportion of OMT CPT codes billed before and after application.

OMT CPT CODE	TOTAL NUMBER OF BILLED CODES BEFORE LEAN MANAGEMENT	TOTAL NUMBER OF BILLED CODES DURING LEAN MANAGEMENT (AUGUST 2018 – MAY 2019)
98925: 1–2 Body Regions	60 (72%)	293 (68%)
98926: 3–4 Body Regions	21 (25%)	112 (26%)
98927: 5–6 Body Regions	2 (2%)	28 (6%)
98928: 7–8 Body Regions	0 (0%)	1 (0.2%)

DISCUSSION

Training to become an independent practicing physician in the context of a three-year residency program requires enhanced knowledge in a variety of areas. The Family Medicine Review Committee (RC) of the ACGME creates the standards for family medicine residents to achieve in a three-year program. Attaining numbers of patient encounters are a requirement. These number requirements ensure that family medicine residents are exposed to various cases that prepare them for practice. From a program standpoint, it emphasizes the importance of teaching residents efficiency in caring for their patients' panel. This efficiency prepares a resident for the real-world capacity to ensure that, along with

the patient's acute needs, the ideals of patient satisfaction, quality and access to care can be addressed. Reports have shown that hospitals or clinics can use Lean management in effective ways to improve efficiency in practice and decrease wait time.^{2,3,5}

Our study exhibits the successes of Lean management in the ambulatory resident clinic setting. The percentage of average visits with prolonged wait times significantly reduced over the short period of implementation using the 5 "S" efficiency method. In the industry world, a 5 "S" tool is used to implement Lean in the workplace. It provides strategies for workers to ensure a clean, organized and efficient environment. These 'S's stand for (as translated from Japanese): Sort (eliminate what is not necessary), Set in order (organize), Shine (clean workspaces), Standardize (schedule maintenance) and Sustain (establish a habit.)³ Recognizing there were many aspects of this memory tool that health care could adapt, the faculty compiled their own tips for efficiency for residents into a similar 5 "S" memory guide. The 5 "S" were taught to residents to follow many of the steps outlined in the Japanese model. Faculty emphasized the 5 "S" of Efficiency in their oversight of residents during the study period to ultimately contribute to the findings.

Similar findings of Lean's effects have been exhibited in other non-family medicine programs.^{4,5} Other studies have shown that putting into play Lean management strategies has shown to reduce the patient wait times, time in a queue and increase satisfaction.¹⁻⁶ While the studies may be limited, other residency programs have also shown similar results and have led to increased involvement of residents in other quality initiatives.⁸ The thought is that the success of Lean is attributed to the ability to identify the issues needing immediate assistance and provide suggestions for improvement in real time.⁵

Throughout an academic year (July through June), it is expected that resident trainees continue to develop skills and improve their performance with time management. For this reason, the results of this study could potentially be questioned in their significance, as the findings attributed to Lean could be solely related to this progression alone in residents. However, the abrupt reduction in wait time that was seen in this study over a one month period from September 2018 to October 2018 would speak against progression alone as the causative factor for the improvement seen in this study.

In addition to these results on patient wait times, OMT use significantly increased the overall percentage of visits after the intervention. It was theorized that having more time in the context of a visit will allow more time to implement OMT seamlessly into visits. While earlier studies indicate that "time constraints" have led to fewer DOs in practice actively using their skills in practice,⁷ more recent information suggests continued high interest in alternative medicine in young learners.⁹ It should be noted that other factors could have influenced the change in OMT used in practice in this study. Throughout the study, the program was implementing a new curriculum for OMT and osteopathic principles and practice while seeking OR status. This could encourage residents to think more osteopathically in their total treatment plan and increase consideration for OMT use. On the other hand, faculty have

emphasized the importance for residents to think holistically in treatment plans as part of their case discussions well before implementing this study or the new curriculum. Analysis of data beyond the study period may help to determine the factor this new curriculum has on implementing more OMT in the clinic moving forward.

Strengths of the study include the novelty of this topic, the attempt to model the intervention on real-world industry successes and the innovative method to study the use of OMT. Weaknesses include the missing data from January, the change in methods throughout the course of Lean (a process that is inherent to Lean itself) and other variables mentioned above, including resident progression and the program's focus on achieving OR status. There may have also been the effect of bias in the study as faculty patient visit data was included throughout. However, because faculty visits were included in both the pre-intervention and post-intervention groups, the effect was likely minimal. Finally, it might have been insightful to single out each 5 "S" to determine individually its impact on the results or how to wait time translated to patient satisfaction scores. However, this information was not available for retrospective review.

Because the current study was performed on residents in training, it was difficult to extrapolate this out to others. Nevertheless, the authors hope that this study might encourage young and experienced physicians alike to trial Lean processes, improve efficiency and help free up more time for OMT. Busy DOs in practice could implement a few of the 5 "S's" with minimal effort and potentially see quick results, as suggested by our study. Future studies might follow residents into private practice to determine if the 5 "S" method continues to affect patient wait time reduction and enhanced OMT use. Studies might also look further into the impact of each 5 "S" on outcomes and the overall effect of 5 "S" on patient satisfaction.

CONCLUSION

This study is rather timely. As family medicine residency programs work to achieve osteopathic recognition, programs will have to find methods to engage residents to ensure the continual practice of osteopathic treatment skills. Our study suggests that the use of Lean may help provide the additional time residents in training needed to improve patients' satisfaction (by decreasing wait times) and use OMT more seamlessly. Challenges in the implementation of Lean included creating buy-in among staff and residents, the time commitment to implementation and the ongoing challenge of creating a standard of work to ensure future success. Nonetheless, the study indicates a method that may help osteopathic programs focus on efficiency and increase OMT use throughout the training.

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CALENDAR OF EVENTS

MARCH 7-8, 2021

DO Day on Capitol Hill
American Osteopathic Association
Virtual
osteopathic.org

MARCH 10, 2021

ACOFP Congress of Delegates
American College of Osteopathic
Family Physicians
Virtual
acofp.org

MARCH 11-14, 2021

ACOFP 58th Annual Convention
& Scientific Seminars
American College of Osteopathic
Family Physicians
Virtual
acofp.org/acofp21

APRIL 15-18, 2021

VOMA 2021 Spring Virtual CME
Conference
Virginia Osteopathic Medical
Association
Virtual
voma-net.org

APRIL 23-25, 2021

Ohio Osteopathic Virtual Symposium
Ohio Osteopathic Association
Virtual
ohioacofp.org

MAY 21-22, 2021

IOA '21 Virtual Live Annual Spring Update
Indiana Osteopathic Association
Virtual
inosteo.org

APRIL 28 - MAY 1, 2021

POMA's Virtual 113th Annual Clinical
Assembly & Scientific Seminar
Pennsylvania Osteopathic Medical
Association
Virtual
poma.org

JUNE 11-13, 2021

KOMA Annual Conference
Kentucky Chapter of ACOFP
koma.org

JUNE 11-13, 2021

MOA 110th Annual Convention
Maine Osteopathic Association
mainedo.org

JUNE 9-13, 2021

TOMA/TX-ACOFP Annual Convention
Texas State Chapter of ACOFP
txacofp.org

JUNE 26-27, 2021

Summer CME
Missouri Society of the ACOFP
msacofp.org

JULY 16-18, 2021

Direct Primary Care Summit
American Academy of Family Physicians,
in partnership with ACOFP
dpcsummit.org

CME Resource: *Osteopathic Family Physician* Offers 2 Hours of 1-B CME

ACOFP members who read *Osteopathic Family Physician* can receive two hours of Category 1-B continuing medical education credit for completing quizzes in the journal. Visit the eLearning Center at www.acofp.org to access the quizzes.

REVIEW ARTICLE

CANNABIDIOL: BACKGROUND AND LITERATURE REVIEW OF POTENTIAL TREATMENTS

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KEYWORDS:

Cannabidiol

Cannabis

CBD

Tetrahydrocannabinol

THC

ABSTRACT:

Cannabidiol, commonly abbreviated CBD, is one of the hundreds of compounds present in the flowering cannabis plant, along with its more well-known structural isomer, Δ^9 -tetrahydrocannabinol or THC. CBD can be extracted from the plant and utilized in many forms, from topical oils to smokable flowers. Recently, availability, interest in and use of CBD across the nation have grown exponentially, with internet searches for CBD increasing 160% between 2017 and 2018 and 14% of Americans citing current CBD use. Users of this compound endorse numerous perceived benefits, including anxiolysis, analgesia and much more. Most users claim to employ CBD to treat specific medical conditions spanning from autoimmune, to psychiatric, to musculoskeletal. Evidence supports some of these reported effects in recent studies, as CBD has demonstrated anticonvulsant, antipsychotic and antinociceptive properties, among others. However, the implications of these findings are still in their infancy. As of June 2018, one FDA-approved pure CBD product for seizure treatment, Epidiolex[®], is available for prescription use and many more are in various stages of testing. However, numerous safety and legal concerns remain regarding off-label and over-the-counter CBD usage. Physicians and other health care professionals are likely to encounter CBD use by their patients. As usage continues to grow, so does the duty of care providers to understand its role and serve as a source of evidence-based information for their community on this relevant health topic.

INTRODUCTION

Cannabidiol, known as CBD, is one of the hundreds of cannabinoid compounds making up the flowering cannabis plant¹ and a new entrant into the health topic spotlight. CBD's more well-known structural isomer, Δ^9 -tetrahydrocannabinol (THC),² is a source of confusion regarding the difference between these compounds and the seemingly sudden popularity and availability of CBD. The body of research regarding CBD is growing and the publicly touted benefits and cure-all promises appear to be growing even faster. The community and media presence of CBD is vast and thus, the responsibility of medical professionals to maintain awareness, follow the research and serve as a source of evidence-based information is paramount.

PLANT SPECIES

CBD and THC, along with many other cannabinoids, coexist in various percentages within cannabis plants. Three plant species are recognized: *Cannabis indica*, *ruderalis* and *sativa*, each containing CBD and/or THC in variable, but sometimes predictable, fractions.³ CBD is created via a decarboxylation process from a cannabidiolic acid precursor and extracted for use.⁴ This compound acts on endogenous cannabinoid receptors in the human body called CB1 and CB2, affecting neurotransmission of GABA, glutamate and serotonin and demonstrating a diversity of pharmacologic actions. These include inhibition of endocannabinoid uptake, transient receptor potential vanilloid 1 activation, G protein-coupled receptor 55 activation and increased 5-HT1A receptor activity.^{5,6} CB1 receptors are located throughout the brain, including the cerebral cortex, hippocampus, basal ganglia and cerebellum, along with other organs such as the lungs, liver and kidneys. CB2 is found mainly in immune and hematopoietic cells.³ This vast distribution of potential sites of action accounts for many claims regarding CBD's effects.

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THC:CBD RATIO

While THC acts as an agonist at CB1 and CB2, CBD acts as a minimal or inverse agonist and non-competitive antagonist at these sites.⁶ This accounts for a key principle in CBD's physiologic actions; pure CBD is non-psychoactive.⁷ The typical high associated with THC is not known to occur with CBD, likely due to antagonism or weak agonism at those same receptors. Therefore, the THC:CBD ratio determines the psychoactive and physical effects of the product, its legal status and even the name of the plant. Cannabis containing a high THC:CBD ratio, with THC greater than 0.3%, are those labeled as marijuana and expected to produce the sensations of intoxication, euphoria and relaxation.³ Plants containing a lower THC:CBD ratio, with less than or up to 0.3% THC, are those often known as hemp⁸ and are the focus of the CBD products that are so readily available in many states today.

POPULARITY

Despite the apparent marketplace novelty of CBD, interest and usage is massive and growing. Internet searches from 2017 – 2018 for CBD increased 160.4% nationally. In an assessment of Google searches in April 2019, CBD surpassed searches for other health topics like veganism, exercise and acupuncture, with 6.4 million CBD searches that month.⁹ A 2019 Gallup Poll reported that 14% of Americans endorsed CBD usage, with the highest density of users in the western United States. The 18- to 29-year-old group were the most frequent users, followed by 30 to 49-year-old. While no gender predilection overall was demonstrated, women used CBD more to treat anxiety and men reported use more for insomnia.¹⁰ In a 2018 cross-sectional study of CBD users, the majority noted use to treat specific medical conditions, most commonly pain, anxiety and depression. Somewhat troublingly, 76% claimed their primary knowledge of CBD stemmed from internet searches or word-of-mouth, demonstrating a potential lack of information available from more reputable sources.¹¹

ADMINISTRATION ROUTES

Administration routes encompass nearly every source of bodily entry. Sublingual is the most common route, usually as a liquid, where CBD is dissolved into sprays, oil droplets and tinctures.¹¹ While some solvents are harmless edible oils like olive, there are reports of products containing CBD dissolved into ethanol or harmful solvents such as naphtha, butane or petroleum.² The oils can be applied topically, absorbed sublingually or ingested in oral capsule form. The hemp flower is utilized like smokable tobacco and sold individually or as blends of various strains alongside effect claims. CBD products for vaporization devices are also available. Additional forms include cosmetics, infused textiles, concentrates utilized in a process known as dabbing and in food products or edibles such as gums, teas, honey, candies or spices.^{3,11,12} These products are easily available online and in CBD stores, vape or smoke shops, pharmacies, grocery stores, gas stations and even pet stores.

TREATMENTS

Interest in CBD stems from beliefs, some unfounded, about the product's benefits or safety, in addition to its massive availability and the curiosity induced by such prevalence. Users tout effects that are desirable, pleasurable or functional. CBD users may desire the believed benefits of cannabis without the high of THC.⁵ Some perceive that CBD is safer versus prescription or nonprescription drugs or that it does not have the addictive capacity. The many available forms allow users to partake via preferred route and some enjoy access to products that are odorless, efficiently dosed (such as the number of drops) or avoid the stigma of being a cannabis user.² Users may note the often legal status as a benefit or the belief that it will not be detected in drug screening. Claims exist of its efficacy as an anxiolytic, antidepressant, antiemetic, analgesic, prophylactic, anti-inflammatory, sedative, energy booster, sexual performance enhancer and natural cure-all. A casual internet search will reveal thousands of books touting CBD's infinite perceived benefits. Assertions of CBD treatment success for neurologic, psychiatric, musculoskeletal, autoimmune, endocrine, gastrointestinal, oncologic and substance abuse disorders saturate the public conversation, whether or not data has been supportive or even researched.

Despite potentially overzealous claims, CBD has demonstrated some physiologic effects due to its action at diverse tissues throughout the body. CBD does demonstrate antiemetic, anxiolytic, anticonvulsant, analgesic, antipsychotic, immunomodulatory and neuroprotective properties, but the clinical implications of these actions are still being delineated.^{3,13,14,15,16} In vitro studies have shown promising anti-tumorigenic properties, as CBD can induce apoptosis, inhibit angiogenesis, decrease free radical production and arrest the cell cycle, similar to several current treatment targets for anti-proliferative therapies.^{2,3} The compound lacks physiologic properties of an addictive substance and no cravings, withdrawal syndromes or compulsive use have been reported.⁴ Low-to-moderate doses show minimal sedation and can be stimulating, but high doses can induce sedation.¹⁷ The contraindications and adverse effects described with accuracy only refer to pure prescription CBD and further studies are needed into the effects of chronic administration.^{18,19} The only known contraindication is hypersensitivity to the compound. The adverse effects include drowsiness, sleep disturbances, skin rash, weight loss, decreased appetite, diarrhea, anemia and increased serum transaminases, infection and asthenia.¹⁹ However, as this only refers to the labeled reactions to prescription CBD, the unregulated products' potential additional effects are unknown.

Seizures

The strongest data support CBD's anticonvulsant properties and thus, it is the only treatment target with an FDA-approved CBD medication.²⁰ This topic gained attention partially due to multiple poignant anecdotal reports by parents of children with seizure disorders describing efficacy in seizure frequency reduction with CBD administration.²¹ However, the therapeutic benefit of CBD for uncontrolled epilepsy has been under evaluation since 1980.⁶ Epidiolex®, approved in June 2018, is indicated to treat the often frequent or intractable seizures associated with Lennox-Gastaut

(LGS) and Dravet (DS) syndromes in patients two years of age or older.¹⁹ This is a 99% pure CBD product,¹⁹ as THC has been shown to have both proconvulsant and anticonvulsant properties,^{22,23} while CBD alone is more consistently anticonvulsant via an only partially understood mechanism.²⁴ In a double-blind, randomized trial with DS patients, Devinsky *et al.* noted a greater reduction in seizure frequency with CBD added to standard antiepileptic therapy versus placebo.²⁵ Similarly, among LGS patients, the addition of CBD to a conventional antiepileptic resulted in greater reductions in the frequency of drop seizures than placebo.²⁶ A 2018 meta-analysis concluded that CBD, in conjunction with other antiepileptic drugs, decreased seizure frequency in patients with DS and LGS, although both had higher adverse events rates than placebo.⁶ While the mechanism is not fully understood, CBD in reviews has demonstrated efficacy as an adjunct to common antiepileptic drugs.²⁷ Epidiolex®, in its novelty, lacks long-term safety data but nonetheless represents a shift in the perspective on cannabinoids as medicine. And while many conditions have been described as targets for CBD application, this remains the only clinically validated indication.

Schizophrenia

Antipsychosis is a known CBD effect, possibly exerted via the facilitation of endocannabinoid signaling and antagonism at CB1 receptors.²⁸ The potential for CBD to reduce both the positive and negative symptoms of schizophrenia has been investigated. Cannabis CBD content has been shown to have an inverse relationship with self-reported positive psychotic symptoms in cannabis users, supporting its antipsychotic potential.²⁹ An overview of treatment prospects for the negative symptoms of schizophrenia noted that CB1 receptor density is correlated with the intensity of negative symptoms and CBD's antagonism at these receptors could account for the reduction of negative symptoms in a small trial of schizophrenic patients.³⁰ Another double-blind, randomized comparison of CBD to the atypical antipsychotic amisulpride demonstrated significant clinical improvement of schizophrenia symptoms. It was well-tolerated with fewer extrapyramidal symptoms, weight gain and prolactin release.³¹ McGuire *et al.* assessed CBD add-on therapy's safety and effectiveness to existing antipsychotic regimens in a double-blind, multicenter, randomized trial of schizophrenia patients, finding lower levels of positive psychotic symptoms at six weeks in the CBD group versus placebo, with similar rates of adverse events. The authors proposed that CBD may represent a new class of treatment for schizophrenia, as it does not appear to depend on dopamine antagonism.³² A 2018 literature review concluded that evidence suggested that CBD may exert antipsychotic effects in patients with schizophrenia. However, the authors cautioned that the antipsychotic effect appeared to be related to endocannabinoid plasma-level increase, not to CBD plasma levels. As endocannabinoid signaling facilitation was the most likely hypothesized mechanism for CBD's antipsychotic effects, continued research into the biochemical action and possible contribution to antipsychotic therapy is warranted.²⁸

Anxiety

While anxiolysis is one of the most endorsed effects of CBD by users, it remains a complex treatment target with mixed evidence-based support. Two pharmacologic mechanisms have been proposed; CBD agonizes 5-HT1A receptors and indirectly potentiates endocannabinoid transmission and both have been linked to the attenuation of defensive responses to threatening or stressful stimuli.³³ CBD has been shown to decrease the number of c-Fos positive neurons in the amygdala, thought to mark neuronal activation and play a role in expressing fear and anxiety.³⁴ Per a 2018 critical overview, CBD may exert an acute anxiolytic effect when administered in a single high dose in patients with Social Anxiety Disorder, possibly related to the modification of cerebral blood flow in the limbic and paralimbic areas or agonism of 5-HT1A receptors.²⁸ According to a recent systematic review, CBD may prove a developing role in alternative treatments for anxiety disorders, demonstrating consistent improved clinical outcomes in Generalized and Social Anxiety Disorders and anxiety related to Post-Traumatic Stress Disorder (PTSD). However, the reviewers noted that small sample sizes limited the majority of studies assessed and that few studies enrolled participants with actual anxiety disorder diagnoses and instead enrolled healthy volunteers modeling anxiety, possibly limiting the generalizability of the results.⁷ Further research evaluating the role of CBD in modulating anxiety disorders is suggested, notably in response to widespread unsanctioned use for this indication.

Substance Abuse Disorders

Recent media reports have proposed a new tool in fighting the opioid crisis: CBD. While the medical literature has not garnered quite the same enthusiasm, there is a growing body of investigation into this hypothesis.³⁵ CBD does possess physiologic activity at addiction-linked pathways, positing a theoretical mechanism for its role in modulating substance abuse. CBD acts on the endocannabinoid system, known to influence drug-seeking behaviors and agonizes serotonergic receptors, which are already pharmacologically targeted for regulating the stress response and compulsive behavior. CBD notably is also an allosteric modulator at μ and δ opioid receptors.³⁶ The reduced amygdala activation during negative emotional processing, as discussed in the anxiety section, also holds the potential to modulate addictive behaviors through dopaminergic and serotonergic effects.⁵

In an interesting correlation, states with legalized marijuana laws report lower numbers of opioid prescriptions, opioid overdoses and opioid-positive screens in motor vehicle fatalities.³⁷ Animal studies have shown CBD to alter drug-seeking behavior and inhibit cue-induced heroin seeking behavior.³⁸ These effects persisted weeks after administration and inhibited relapse behavior even when administered during heroin intake, suggesting that CBD could affect relapse prevention after periods of abstinence.³⁷ Even in a sensitive population of polydrug abusers, administration of a therapeutic dose of CBD failed to elicit significant abuse potential versus placebo. It showed significantly less abuse-related effects than the positive controls, dronabinol and alprazolam.³⁹ In a systematic review of CBD as an intervention for addiction, the authors concluded that it might benefit opioid addiction by decreasing drug-seeking behavior and reducing the reward-facilitating effects during intoxication.³⁶

Another review revealed several studies supporting the protective effects of CBD on addiction to psychostimulants, including reduction of the detrimental neural effects of cocaine and long-lasting prevention of cocaine and methamphetamine-seeking behaviors, but with controversial consistency in the results.⁴⁰ CBD has even been implicated in reducing the number of cigarettes consumed by smokers, but no data was found supporting alcohol abuse intervention.³⁶ A notable shortcoming limiting generalizability across this body of data is the scarcity of human trials.

Alzheimer's Disease and Parkinson's Disease

Unfortunately, neurodegenerative disorders represent ideal targets for pseudoscientific claims to reverse these irreversible and debilitating disease processes. Still, evidence for CBD's effects on Alzheimer's Disease (AD) and Parkinson's Disease (PD) manifestations poses an interesting hypothesis currently being investigated. Proposed mechanisms include reducing tau protein hyperphosphorylation, attenuation of neuroinflammatory markers, reduction of reactive oxygen species, counteraction of proinflammatory cytokines and attenuation of beta amyloid peptide effects in the hippocampus, modulation of microglial cell function and reversal of iron-induced neurodegeneration.^{41,42,43,44,45} A 2014 study was the first to demonstrate that CBD prevented the development of social recognition deficits in AD in transgenic mice and hypothesized its potential to treat the devastating social withdrawal and facial recognition deficits.⁴⁶ Regarding PD, the effects of CBD on physiologic mechanisms and markers of functional improvement have been described in the literature. Pathways implicated include attenuation of oxidative stress and neurodegeneration of nigrostriatal dopaminergic neurons.⁴¹ Specific to disease morbidity, a double-blind exploratory study noted a possible improvement in the quality of life measures, including functioning and well-being, in CBD-treated PD patients versus placebo.⁴⁷ However, a mini-literature review in 2018 cited a lack of support for improvement in motor symptoms of PD following CBD treatment and noted a potential role for prevention rather than treatment based on animal studies.⁴⁸

Chronic Pain

Another commonly endorsed reason for CBD use, chronic pain, represents a complicated and varied treatment target. Cannabis has historically been claimed to have analgesic effects, but pure CBD is a newer entrant into the conversation. CBD is touted anecdotally to treat many types of pain, but insufficient and inconsistent evidence exists for its recommendation.¹² Possible explanatory models include anti-inflammatory properties, suppression of lymphocyte proliferation, blockade of reactive oxygen burst by granulocytes, regulation of pain perception and inhibition of the lipopolysaccharide-induced increase in serum tumor necrosis factor.^{49,50} Evidence across literature reviews indicates that cannabinoids produce antinociceptive effects in inflammatory, myofascial and neuropathic pain in rodents; however, animal models dominate the body of research.^{15,51,52} CBD-induced analgesia in humans has not been extensively studied and a 2017 overview of systematic reviews on this topic consistently found insufficient evidence of any cannabis-based

medicine for pain management in patients with rheumatic disease and cancer.⁵³ A recent review also confirmed a lack of high-quality research investigating CBD for human musculoskeletal disease.⁵⁴ As there are no pure CBD pharmaceuticals approved for pain therapy, most research on this topic involves products containing THC/CBD combinations, limiting any attribution of effect to CBD alone.⁴⁹ Clinical trials on the subject are limited by small sample sizes, inconsistent cannabinoid types and dosages and variable assessments of pain.⁵⁰ Given the medical landscape shift towards non-opioid pain management options when appropriate, this area of cannabis research is deserving of future academic attention.

Sleep Disorders

While administration of medium- and high-dose CBD can cause sedation, evidence for its use as a sleep aid is mixed. The endocannabinoid system's role in the circadian sleep-wake cycle may be implicated, but an understanding of the mechanism is not complete.¹⁷ Administration of CBD has been linked to increased total sleep time in rat models and possible sleep effects in combination with THC in young adult humans.^{55,56} Isolated studies have tested specific sleep indications but reviews have not supported any broad, substantial benefit. A 2016 case study described a pediatric victim of sexual abuse, suffering from PTSD and refractory insomnia. They experienced increased sleep quality and quantity without noted adverse effects after a CBD oil administration trial.⁵⁷ Another small, non-placebo-controlled case series of PD patients demonstrated a rapid, significant and sustained reduction in the frequency of REM sleep behavior disorder symptoms after CBD treatment.⁵⁸ However, a large retrospective case series found improved sleep scores after one month of CBD treatment but the improvement was not sustained over the three-month study.⁵⁹ CBD was additionally not found to alter the sleep-wake cycle versus placebo as measured by polysomnography, subjective and cognitive measures in a randomized, double-blind crossover trial of healthy patients.⁶⁰ Again, much of the available research was conducted in animal models or with cannabis products containing THC and CBD, limiting the knowledge of CBD's effects alone.

SAFETY CONCERNS

Regardless of the evidence surrounding indications, CBD is widely available and use is increasing. Projections of retail sales of CBD products are estimated to be as great as \$1.9 billion by 2020. Therefore, a discussion of the safety concerns is necessary. Per the World Health Organization's 2018 Cannabidiol Critical Review Report, *"to date, there is no evidence of recreational use of CBD or any public health-related problems associated with the use of pure CBD."*⁴ Pure CBD is well-tolerated at up to 1500 mg per day with a favorable safety profile confirmed in a review of clinical data.^{18,19,22} However, CBD does inhibit cytochrome P450 both *in vitro* and in animals, representing a concern for many conceivable drug interactions.^{18,22,61} A case report detailed a 44-year old male on chronic warfarin therapy whose International Normalized Ratio (INR) increased with up-titration of CBD oil.⁶² Oral absorption has also been shown to increase when taken with high fat or high-calorie meals due to its high lipophilicity.^{19,22} In

laboratory animals, hepatocellular injury and developmental and reproductive toxicities have been demonstrated. CBD use is not recommended during pregnancy in response to adverse events described in animals. In humans using non-medicinal cannabis, it has been detected in the umbilical cord.^{6,63} The risk of passage into breastmilk is currently unknown.¹⁹

The most concerning risk may be the unknown production, composition and quality of non-pharmaceutical CBD. Cannabinoid analysis can differ significantly between testing labs and there are no generally accepted guidelines or laboratory certification qualifications. Contaminants have been reported, some of which could have potential health outcomes, including pesticides, synthetic cannabinoids, heavy metals, molds, bacteria and aflatoxins. Some samples have shown levels of non-decarboxylated cannabinoids, which have not undergone the typical extraction process and effects of these precursors in vivo have not been studied thoroughly.² The THC:CBD ratio often can deviate from the label, which raises many concerns, including intake of undesired THC levels, legal implications, sub-therapeutic CBD dosages or unwanted or adverse THC effects.

In a Dutch study,⁴⁶ cannabis oil samples, obtained online or from home stores, were tested versus their labeled THC and CBD percentages. Seven samples were devoid of any cannabinoids and several drastically diverged from their labeled concentrations, with percentage differences of CBD up to 100%. Others contained more THC than indicated by their packaging, with one sample containing 57.5% more.⁶⁴ An American analysis of 84 CBD products from 31 online retailers reported equally disconcerting mislabeling, where 42.9% were under-labeled for CBD content, 26.2% over-labeled and 21.4% had THC content sufficient to potentially induce intoxication or impairment.⁶⁵ These results not only pose potential health risks but also raise concern for implications in drug screening. While pure CBD intake is not known to result in a positive urine drug test by federal workplace guidelines, CBD products that include THC, perhaps unknown to the user, can produce positive urine screening results.⁶⁶

Cannabis has a long and convoluted history with the legal system, the intricacies of which are beyond the scope of this discussion. Per the *Controlled Substances Act*, marijuana and its compounds and derivatives, including cannabinoids, are classified as Schedule 1 substances. However, the Agriculture Improvement Act of 2018, the so-called Farm Bill, removed hemp, defined as the cannabis plant or any part thereof containing less than or equal to 0.3% THC, from the definition of marijuana and categorization as a controlled substance under federal law.²¹ This largely accounts for the noticeable expansion in CBD availability, but individual state cannabis access laws vary widely. They range from the prohibition of all cannabis, including CBD, to full adult and medical cannabis use programs, adding to the ambiguity about purchase and consumption. Regulatory concerns further complicate the dialogue, especially regarding its status as a medicine or natural food product.

This classification changes the regulation, as medicines are considered unsafe until proven safe, but food products are considered safe until shown otherwise.² Per the FDA, under the *Federal Food, Drug and Cosmetic Act*, CBD is excluded from the

definition of a dietary supplement and unsubstantiated medical claims are prohibited. The FDA issued *Warning Letters* in 2015 and 2016 to online vendors in violation of these terms for misbranding CBD products with medical claims or mislabeled contents.⁶⁷ However, enforcement depends on resources to do so and the threat posed to public health, explaining some of the widespread accessibility.⁸ Age limit to purchase is variable depending on the state and individual vendor policies.

CLINICAL TRIALS

Clinical trials abound in this time of massive influx of CBD information and prevalence of use. Pharmaceuticals are in various testing phases for a diverse list of new indications. Pure CBD in tablet, transdermal gel, sublingual oil, powder, aerosolized inhalant and intravenous formulations are facing research scrutiny for future potential medical application. Trials are underway for expanding the anticonvulsant indications, including other treatment-resistant epilepsies, absence seizures, Sturge-Weber Syndrome, Tuberous Sclerosis and infantile spasms.^{4,27,68} The list of additional medicinal CBD products in development is expansive and includes hypothesized indications for Fragile X Syndrome, marijuana adverse event prevention, Graft-Versus-Host Disease prevention, schizophrenia, encephalopathy and Prader-Willi syndrome.^{4,69,70} Theoretical proposed treatment targets based on preliminary studies represent an even larger body of intriguing future research directions, including many psychiatric disorders, autism spectrum disorders, diabetes mellitus complications, inflammatory bowel disease, post-ebola syndrome and pain management.^{71,72,73,74,75} The body of evidence is growing and represents an area of necessary attention for health care professionals to provide current and informed evidence-based medicine.

CONCLUSION

The advice for clinicians remains to be vigilant for high-quality studies and evidence. The current body of research on cannabinoids is ever-changing and it is the duty of practitioners to follow and critically evaluate the data. Consider asking patients about their CBD use, specifically when obtaining a social history. Document quantity, frequency and route if known. Ask patients their purpose for the use, as it may facilitate discussion of a formerly unrevealed medical concern. Offer alternatives if a patient is using CBD to treat a specific symptom and utilize the conversation as an opportunity to educate and discuss potential effective therapies. Inform patients of potential risks, including adulteration of CBD products, scarcity of evidence for non-pharmaceutical use, drug interaction risks and potential legal concerns due to inconsistent labeling. Remain non-judgmental and unbiased to better facilitate a patient-physician partnership to approach their concerns and rationale for use. As more evidence becomes available, being a source of reputable information for patients remains a high priority and a necessity to protect and improve the health of the community.

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REVIEW ARTICLE

MINDFULNESS: PRINCIPLES AND APPLICATION TO DECREASE OPIATE USE IN PRIMARY CARE WITH AN OSTEOPATHIC COMPONENT

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ABSTRACT:

Mindfulness is a focused approach toward accepting one's thoughts without judgment or perseveration, with ancient Indo-Sino-Tibetan philosophical origins. Many variations exist; however, they typically include focused attention where one concentrates on a specific sensation such as breathing and open monitoring where one concentrates on consciousness itself. Mindfulness-based interventions (MBIs) are specific, organized, targeted methods to teach mindfulness with specific goals.

MBIs have shown benefit in pain patients. MBIs teach the individual the concept of pain coping, encouraging cognitive flexibility and attempting to discourage the fear or alarm reaction of pain, instead focusing on the quality of life and functionality. Mindfulness-based stress reduction (MBSR) showed a 30% significant improvement in pain intensity and pain coping at six months in patients with chronic low back pain, compared to opiates and NSAIDs, which showed no benefit.

MBIs have also shown benefit in addiction, as they help the individual relearn to control cravings, habit modification and attempt to restore the natural reward system while improving regulation of emotions. Applications to opiate use disorder are significant as patients learn to enjoy the lifestyle of recovery and learn to believe they can improve. Additionally, other comorbid conditions are known to improve with MBIs and mindfulness-based principles support the holistic principle of mind, spirit and body consistent with osteopathic medicine.

INTRODUCTION

Mindfulness is a focused approach toward acceptance of one's moment-by-moment thoughts, sensations and cognitions, without judgment or perseveration,¹ that is commonly described as a state of purposeful, metacognitive awareness.² It is thought to be derived from various origins, including the ancient Indo-Sino-Tibetan philosophies,¹ and Vipassana, Buddhist and Zen practices.² The main objective of this manuscript is to describe mindfulness, provide an overview of basic approaches and interventions and discuss applying these principles into primary care, with foci on both pain control and opiate addiction² in an effort to reduce opiate use.

BASICS OF MINDFULNESS MEDITATION

Mindfulness meditation is a label given to any episode in which an individual uses the mindfulness principles. Though many variations exist, common teachings start with one finding a quiet space with limited distractions, sitting in a firm chair with feet flat on the floor and hands resting on the knees, palms up. A common alternative is with one sitting on the floor with legs crossed and hands on the knees.

A typical episode begins with focused attention in which an individual concentrates on one sensation in an effort to disengage from others. A common practice for the individual is to focus on his or her breathing, down to the detail of how each breath comes and goes. This may progress to a body scan using the same focus to proceed through one's entire body. This centers the individual on specific interoceptive and proprioceptive sensations. A surrogate may be an external focus, but with the same bottom-line goal of disengaging from other thoughts, emotions and distractions.¹

Open monitoring commonly follows where one will begin to concentrate on consciousness itself, especially the temporality of thoughts or how quickly they come and go.¹ As one goes through these steps, the goal is to reveal how a particular flow

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of consciousness is momentary and unending. Though there is variation, typical sessions will begin with focused attention then transition to open monitoring. Each session's duration may vary per person and goal, though it is common for learners to start with 5–10 minutes daily, then increase the time spent and frequency as one becomes more comfortable.¹

At the early stages of practicing, individuals will begin to engage and enhance the top-down regulation of lower-level afferent processing by forcefully refraining from further processing of judgmental and ruminating emotional stimuli. It is important to discuss the Monitor and Acceptance Theory posed by Lindsay and Creswell (2019), positing that mindfulness training encompasses a continuum of two concepts. Mindfulness awareness reflects tending to present experiences at the moment, while mindfulness acceptance describes the attitude of recognizing a current experience without judgment. This is a significant distinction as it is important to teach both concepts together; mindfulness-awareness without mindfulness acceptance may increase distress.³

As episodes become more common, a decoupling between the sensory process and assessments or judgments will occur.⁴ This will allow one to remove the automaticity that commonly results from pain or addiction, instead permitting one to become accepting and nonreactive towards distressing thoughts and emotions.¹ Frequent and thoughtful practice cultivates increased internalized attention,⁴ and ultimately, the concept of trait mindfulness, which is a durable mindset of purposeful, mindful principles during life's everyday challenges.¹

Mindfulness-based interventions (MBIs) are commonly used to include all intervention methods and application of the mindfulness principles, but each with a targeted approach and goal. Many sources refer to MBIs as self-cognitive behavioral therapy methods or mental training designed to exercise and renew dysregulated neurocognitive processes.^{5,6} They allow focusing on the etiology of thoughts, how to control them and understanding one's reactions to them without perseveration while focused on specific targets such as stress, recovery or relapse prevention.^{1,4,7,8}

TABLE 1:

Brief description of mindfulness-based interventions (MBIs)

Mindfulness-Based Stress Reduction (MBSR)	Most common MBI. Eight weeks long with a workbook and daily homework assignments. Requires a trained professional. Typically has a one-day silent retreat. ^{2,8,11,12}
Mindfulness-Oriented Recovery Enhancement (MORE)	Eight weeks long. One session per week combining mindfulness and cognitive behavioral therapy. Focusing on positive influence and social support. ^{1,9,10}
Mindfulness-Based Relapse Protection (MBRP) ^{1,7,13}	Eight weeks long. Group therapy. Self-monitor cravings and negative affect. ¹ Reduces impulsivity, relapse. ¹³ Prepare patients for environmental relapse risks. ⁷
Mindfulness-Based Cognitive Therapy (MBCT) ^{1,14}	Eight weeks long. Two hours per week. ¹⁴ Focus on responding to negative thoughts and emotions. ²
Mindfulness-Based Therapy (MBT) ⁵	Based on MBSR and MBCT. Three-week period with twice-weekly group classes and daily practice. ⁵
Mindfulness-Based Cognitive Behavioral Therapy (MBCBT) ²	Contemporary interpretation of mindfulness and Cognitive Behavioral Therapy. ²
Mindfulness-Based Acceptance and Commitment Therapy (MBACT) ¹⁵	Focus on overcoming negative thoughts and feelings. Focus on accepting difficulties and being active to improve outcomes. ²
Mind-Body Skills Groups (MBSG)	Mind-body skills, including mindfulness intervention and meditation. Ten weeks. Groups of 8–10 participants. Two hours once a week, with a one- and two-months booster. ¹⁵

APPLICATION TO PAIN CONTROL

Mindfulness application to pain control can be extremely effective, though difficult to interpret or give specific recommendations given heterogeneous studies with varied complaints. A Cochrane review stated in 2013 the incidence of chronic pain in America was 11.2%.¹⁶ Later, a 2019 Cochrane review reported 20% of adults suffer from chronic pain not caused by cancer.⁹ Additionally, the CDC guideline recommends pursuing non-opiate pharmacologic treatments and alternative therapies as the first line for chronic pain^{2,17} with a focus on mindfulness.

It is important to understand the concept of illness expectations, often interpreted as nothing can be done to help, which demonstrates cognitive rigidity. MBIs focus on teaching cognitive flexibility through illness perceptions, the alternative that behavioral change can alter the sensations experienced.¹⁸ Additionally, many sources voice fear or alarm reaction of pain, which can make the perception of pain worse and lead to other physiologic changes such as increased muscle tension. Sources focused on pain sensation do show that mindfulness-meditation induced pain relief is associated with a reduced thalamic activity, which may further attenuate low-level sensory processing.^{2,19}

Mindfulness modalities teach to focus on pain coping¹¹ concentrating on the quality of life and functionality of an individual, rather than the pain perception itself.² A brief three-day Randomized Control Trial (RCT) with mindfulness meditation was effective in reducing pain ratings to experimentally-induced pain.¹² A 2015 Cochrane review for fibromyalgia showed that psychological intervention therapies (including mindfulness) have low-quality evidence of improving physical function, pain and mood for adults compared to control.

Chronic low back pain (cLBP) is the most common long-term noncancer pain for which long term opioids are prescribed,⁸ and is the leading cause of disability in America.²⁰ Morone (2019) showed that MBSR had a 30% improvement in pain intensity and pain coping at six months and beyond with cLBP patients, contrasted with opiates and NSAIDs, which showed no benefit.¹¹ The American College of Physicians now recommends MBSR for

cLBP as one of thirteen nonpharmacologic therapies.^{2,8,21} One RCT showed after 26 weeks that adults with cLBP, treated with MBSR and compared with CBT and usual care, had improvement in pain and function with MBSR compared to usual care, but no significant difference between MBSR and CBT. This suggests both treatments are equivocal.²²

Another pilot, 26 weeks RCT, assessed meditation-CBT intervention, mindfulness for chronic pain among cLBP with long term treatment of opioids. At 26 weeks, there was a significant improvement in pain intensity, reduced pain sensitivity, with a dose-responsive decreased pain sensitivity to noxious thermal stimuli at eight and 26 weeks, suggesting meditation-CBT reduced CNS sensitivity and hyperalgesia. The improvements in physical function, pain acceptance and inflammatory biomarker profile did not reach statistical significance but did favor the meditation-CBT group.⁸ And further, a pilot study on mindfulness-based therapy showed a significant decrease in chronic tension-type headache frequency but not intensity or duration.⁵

APPLICATION TO OPIATE ADDICTION

A Cochrane review stated in 2013 that 1.9 million Americans abused or were dependent on opiates.¹⁶ Addiction encompasses automatic, habitual or stereotyped responses, without conscious volition, free will or regard for consequences. Addiction is thought to occur secondary to neural dysregulation from substance abuse leading to a cycle of cravings and compulsivity.^{1,23} In short, addiction can be considered mindlessness or the direct opposite of mindfulness.^{1,2,7} Cravings are considered strong desires that intrude and overwhelm to use a drug, while a pleasant reward memory is superimposed on a negative emotional state.⁷ Positive emotions from the drug-liking effect cause a negative effect of reinforcement and are thought to cause neurobiological changes such as atrophy of the prefrontal cortex and its cognitive control networks.^{1,23}

Cravings can be further described to include tonic cravings or background cravings, which occur in the absence of outside factors or triggers, typically from underlying negative effects from abstaining or withdrawal. Phasic craving, also known as cue-induced, describes specific triggers or events that initiate a craving.⁷ Teaching mindfulness focuses on countering these addictive behaviors, working towards habit modification, attempting to restore the natural reward system, improving regulation of emotions and increasing distress tolerance.⁴ It aims to teach acceptance and non-judgment as described above and has been shown to reduce cravings overall, both underlying tonic cravings as well as preparing individuals to accept and cope phasic cravings from environmental cues and triggers. It works by encouraging bottom-up control, modifying the perception and understanding of cravings and negative affect, as well as top-down control by having control over behavioral response to cravings.^{24,25}

This cognitive control can strengthen the medial and lateral prefrontal cortices,²⁶ thereby improving self-control, responding to inhibition, improving thoughtful decision-making, reducing stress and preventing relapse.¹ One study showed additional structural changes, such as reducing gray matter in the amygdala,

part of the impulsive system, with concomitant increases in gray matter concentrations of the hippocampus, responsible for learning and memory.⁷ A Cochrane review in 2017 demonstrated inconclusive results with MORE with Addiction⁹ with low quality. An ultra-brief primary care study with MBSR showed promise for reducing actual substance use, cravings and relapse rates over 12 months.²⁴

Opiate use disorder is a chronic and relapsing condition of negative affect, craving and impulsivity.^{7,11} Many MBIs can be used to assist OUD patients. As they begin to learn mindfulness, patients often mention the appeal of non-pharmacologic treatments allowing them to enjoy the lifestyle of recovery rather than living in an abnormal state of being an addict.²³ The most important aspect is that the patient believes they can improve and commit to recovery.²³ The mindfulness principles will encourage focusing on positive outcomes such as dealing with stress, finding peace and improving one's motivation to remain in recovery.¹⁰ MBSR has been shown to reduce cravings, relapses and substance use.²⁴

EFFECT ON COMORBID CONDITIONS

A patient's medical and psychiatric history can profoundly affect the perception of pain and addictive cues and ultimately contribute to relapses. Various studies with comorbid conditions show both pain patients and addiction patients have improvement and a more positive outlook upon learning mindfulness.²⁴ Mindfulness has been shown to improve anxiety, depression, sleep, schizophrenia and other comorbid psych illness, all common risks for worsening pain and increasing the chance of relapse.^{4,8,24} A systematic review of mindfulness meditation for SUD supports reducing comorbid psych conditions including depression, anxiety and stress.²⁴ A study on PTSD shows a decrease in hyperarousal and avoidance, with improved anger control and sleep.¹⁵ A study with MBSR showed a marginally greater decrease in cortisol levels collected at 35 and 60 minutes post-stressor onset. Though not specific, this may support overall decreased stress levels in these patients.²⁰

OSTEOPATHIC COMPONENT

The founding father of osteopathy, A.T. Still, in his early writings, wrote that the human body is a "delicate and perfect machine" with osteopathic physicians having the task of correcting or reestablishing this fine balance. He felt one should find the cause first, "He [the osteopath] should go back to the cause which when corrected results in a disappearance of the effect."^{15,27} He felt the opioid epidemic of his time after the Civil War was worsened by focusing on the pain and addiction, not the cause of symptoms.²⁷ Mindfulness aims to realign the focus on pain and addiction, the origin of sensations and the holistic principle of mind, body and behavior interconnectedness,²⁸ key components of osteopathic medicine.

BARRIERS TO USE

Initially, many patients are resistant to accepting the benefits of any therapy that is not pharmacologic and the most important ingredient is the person committing and believing they can improve.^{11,23} A key point to discuss with patients early on is MBIs may make symptoms worse, as they encourage the patient to focus on the symptoms.² Educating that this increase is only temporary is extremely important.² Additionally, the individual may have a lack of immediate benefit and must comprehend that there is a significant time investment.^{1,10,24} Other challenges include the feasibility of finding an appropriate practitioner, difficulty building relationships with the person teaching MBIs and finding adequate, quiet space.^{10,24} The most important step is informing the patient regarding the long-term benefits.

APPLICATION TO PRIMARY CARE

To apply the basics described above, one must understand the basics of mindfulness, develop and understand high-yield steps to teach patients and address the underlying issues. There are many workbooks that providers can recommend to patients as a start. A single-group, cohort pilot study involving three family practice physicians, all trained in mindfulness meditation, performed ultra-brief interventions to OUD patients, including scripted, timed, educational sessions lasting 10–12 minutes, with handouts and audio exercises. Results revealed greater cognitive control over cravings and negative emotions at two, four-and six-months follow-ups, with a statistically significant difference in the relapse rate between higher uptakes of home mindfulness practice with possible confounders.²⁴

CONCLUSION

Mindfulness basics and MBIs show promise in decreasing pain perception, the sensation of addiction cues and ultimate opiate use. A variety of studies do support the use, though most with low-quality evidence. The family practitioner can benefit from learning these basics and trying to teach patients while awaiting more direct studies with higher quality evidence.

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REVIEW ARTICLE

NONALCOHOLIC STEATOHEPATITIS: CASE-BASED FOCUSED ON PEDIATRIC AND ADULT GUIDELINES

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ABSTRACT:

Nonalcoholic fatty liver disease (NAFLD) comprises a continuum of conditions associated with insulin resistance and obesity in the absence of secondary causes of hepatic steatosis (alcohol, medication, genetic disorders, hepatitis, etc.) The milder, benign form of NAFLD is simple fatty liver or steatosis. Fatty infiltration affects more than 5% of the liver.¹ This is determined by histologic exam, direct quantification or imaging. The range progresses to nonalcoholic steatohepatitis (NASH) and culminates in fibrosis and cirrhosis. Histologic changes include ballooning degeneration of hepatocytes, the presence of Mallory bodies, macrovesicular steatosis, lobular or portal inflammation.²

NAFLD is now the foremost cause of childhood, adolescent and adult chronic hepatic disease. The pediatric and adult obesity epidemic makes NAFLD a potentially ubiquitous hepatic pathology amongst all patients.^{3,4,5} The increase of obese children and adults with obesity correlates to the rise of NAFLD cases. In adults, the rate of NAFLD increase is paired with the epidemics of obesity and Type 2 Diabetes (T2DM).^{4,5} Data proposes hepatic-related mortality may be due to NASH ultimately progressing to cirrhosis.^{3,4} NAFLD is linked to pediatric and adult cardiovascular risk and morbidity.^{4,6} Non-invasive biomarkers and the gold standard of liver biopsy not only diagnose but assist in targeted therapies.⁶ Most pharmacologic therapy for NAFLD is in trial stages for patients of all ages. Pioglitazone is favored in adults who have NAFLD/NASH and T2DM.⁷ The gut biome is also impactful. Lifestyle modifications of diet and exercise can reduce the public health burden of this disease.^{7,8,9,10}

INTRODUCTION

The prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) among adults and children has increased worldwide.⁵ There is a 34% prevalence among children with obesity vs. 7% in the general pediatric population.² The classic clinical presentation of NAFLD in the pediatric population typically occurs in patients with obesity or overweight, with a male predominance in the prepubertal age group and a higher occurrence in Hispanic origin. Dyslipidemia can have multiple contributing environmental and genetic influences, such as nutrition, physical inactivity, socioeconomic levels, tobacco exposure, etc. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) commissioned a multidisciplinary committee with vested interests to put forth recommendations surrounding

screening, diagnosis and pediatric treatment Nonalcoholic Steatohepatitis (NASH). These recommendations will be further discussed in the pediatric case.¹¹

The worldwide prevalence of NAFLD and NASH in adults is estimated to be 25% and 3-5%, respectively.^{12,13} The clinical presentation of NAFLD in adult patients also parallels metabolic conditions, including diabetes mellitus, dyslipidemia and obesity.⁹ Screening patients for NAFLD in this disease setting is not standardized. Other extra-hepatic diseases associated with NAFLD include obstructive sleep apnea, psoriasis, osteoporosis, polycystic ovarian syndrome, primary hypothyroidism, chronic kidney diseases and extra-hepatic cancers.⁷ According to Leoni *et al.* in a systematic review of five international guidelines, including the American Association for the Study of Liver Diseases (AASLD), NAFLD screening is approached differently. Only three of the five international guidelines recommend screening "high-risk groups," whereas the AASLD suggested that screening adults with several metabolic risk factors was not cost effective. The European Association for the Study of the Liver (EASL) recommended screening in patients with obesity, metabolic syndrome and abnormal liver enzymes. The National Institute for

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Health and Care Excellence (NICE) and the Asia-Pacific guidelines both recommended screening in patients with obesity and T2DM.

The pathogenesis of NAFLD is poorly defined, yet the persistent “two-hit process” seems to be the most likely hypothesis.^{8,14} Lipid accumulation in the liver is most likely due to insulin resistance and hepatic steatosis development. Insulin resistance and ultimate hyperinsulinemia lead to changes to hepatic-free fatty acid uptake, synthesis, degradation and secretion promoting increased triglyceride presence in hepatocytes. This allows the liver to be vulnerable to the second hit—progressive liver damage resulting from the inflammatory response (oxidative stress from dysfunctional mitochondria and proinflammatory cytokines, like TNF-alpha). These contributing factors promote the progression from simple fatty liver to steatohepatitis and ultimately, cirrhosis.¹⁴

A leading hypothesis proposed a way to limit progressive liver damage by altering the TNF-a pathways.¹⁴ This action will improve insulin sensitivity and reduce steatosis, thereby lowering the free fatty acid levels.¹⁴ One way to augment this process is with the help of protective factors, such as adiponectin. Adipocytes secrete adiponectin at a rate inversely proportional to the BMI level.^{8,14} This reinforces the need for lifestyle modifications that lower BMI as a mainstay of treatment.

This article will highlight the approach for pediatric and adult patients with increased risk for NAFLD and co-morbid diseases, including current and future testing and treatment discussions. Among the pediatric and adult patients with risk for NAFLD, many imaging techniques, biomarkers and lifestyle recommendations are similar. Considering the increased mortality with metabolic syndrome and cardiovascular disease in adult patients with NAFLD, medications will be highlighted that are not used in the pediatric population.

CASE 1

A 12-year-old Hispanic male presents for his annual physical exam. He has no significant past medical history. He endorses right upper quadrant pain as well as fatigue. His mother denies snoring or apnea. He endorses a sedentary lifestyle and consumes a diet replete with junk food with little to no fresh fruit or vegetables. His BMI is 30.9, placing the BMI-for-age at the 99th percentile for boys aged 12 years. His blood pressure is 124/82mmHg. He has noted hepatomegaly, acanthosis nigricans on his neck, abdominal striae and obese body habitus on exam. The results of his fasting lipid panel are: total cholesterol 204 mg/dL, LDL-C 140 mg/dL, HDL-C 28 mg/dL and non-HDL-C 150 mg/dL. His triglycerides are 136 mg/dL and albumin is normal at 4 g/dL. His serum alanine aminotransferase is 32 U/L and aspartate aminotransferase are moderately elevated at 30 U/L with a normal AST: ALT ratio of 0.94. Ultrasound of the liver demonstrates a diffuse echogenicity due to the fatty infiltration. His Hgba1c is 5.7%, indicating an increased risk for diabetes, fasting glucose 145 mg/dL causing concern for pre-diabetes: GGT 20 U/L (normal) bilirubin 1.3 mg/dL, additionally, a PHQ-9 is performed that demonstrates a score of moderate depression, without suicidal ideation.

For this 12-year-old male, his epidemiologic risks include his age, gender and ethnic origin. His elevated BMI and blood pressure, as well as hyperinsulinemia, pose further risks.

The NASPGHAN GRADE System (Grading of Recommendations, Assessment, Development and Evaluation) is utilized to stratify both the strength of the recommendations and the evidence quality for screening, diagnosis and treatment. Below are two tables (Tables 1 and 2) of the data extrapolated from both an evidence-based approach and the clinical acumen of the panelists.

TABLE 1:

Screening recommendations based on NASPGHAN Clinical Practice Guidelines for diagnosis and treatment of Nonalcoholic Fatty Liver Disease in children.¹¹

STRENGTH OF RECOMMENDATION	QUALITY OF EVIDENCE	RECOMMENDATION
1	B	Ages 9– 11 years old for all children with obesity (BMI≥95th percentile) and children who are overweight (BMI≥ 85th and <94th percentile) with risk factors (insulin resistance, central adiposity, pre-diabetes, dyslipidemia, sleep apnea or family history of NAFLD/NASH).
2	B	Earlier screening in younger patients if family history of NAFLD/NASH, severe obesity or hypopituitarism.
2	C.	Screening of siblings and parents of children with NAFLD if known risk factors (obesity, Hispanic ethnicity, insulin resistance, pre-diabetes, diabetes, dyslipidemia).
1	B	The best screening test for NAFLD in children is ALT, but it does have substantial limitations.
1	A	ALT interpretation should be based upon sex-specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys) not individual laboratory upper limits of normal.
1	C	Persistently (>3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD or other causes of chronic hepatitis.
2	C	ALT >80 U/L warrants increased clinical concern and timely evaluation.
2	C	Follow-up screening for NAFLD is recommended.
2	C	When the initial screening test is normal, consider repeating ALT every two to three years if risk factors remain unchanged.
2	C	Consider repeating screening sooner if clinical risk factors of NAFLD increase in number or severity. Examples include excessive weight gain, T2DM or OSA.

TABLE 2:

Diagnostic recommendations based on NASPGHAN Clinical Practice Guidelines for diagnosis and treatment of Nonalcoholic Fatty Liver Disease in children.¹¹

STRENGTH OF RECOMMENDATION	QUALITY OF EVIDENCE	RECOMMENDATION
1	A	Exclude alternative etiologies for elevated ALT and/or hepatic steatosis and investigate the presence of coexisting chronic liver diseases.
1	B	Liver biopsy should be considered for NAFLD assessment in children who have increased risk of NASH and/or advanced fibrosis, such as higher ALT (>80 U/L) splenomegaly, AST/ALT >1, panhypopituitarism, advanced fibrosis and T2DM.
1	B	Ultrasound is not recommended for the determination or quantification of steatosis due to poor sensitivity and specificity. Ultrasound may be useful for assessing other causes of liver disease, such as masses gallbladder disease, changes associated with portal hypertension, etc.
1	B	The use of CT is not recommended for the determination or quantification of steatosis due to radiation risk.

Strength of recommendation (Tables 1 and 2)

Strong [1] Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-reported outcomes and cost. Weak [2] Variability in preferences and values or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

Quality of evidence (Tables 1 and 2)

High [A] Further research is unlikely to change confidence in the estimate of the clinical effect. Moderate [B] Further research may change confidence in the estimate of the clinical effect. Low [C] Further research is likely to change confidence in the estimate of the clinical effect.

There is an elevation in insulin levels during Sexual Maturity Rating 2, typically around age 8–15 years old with the development of secondary sexual characteristics. This hormonal change may enhance liver fat accumulation. It is unclear if a sedentary lifestyle coupled with poor food choices in the adolescent period can fully explain elevated rates of NASH in this age group.⁶ Screening can begin between 9–11 years old for children with obesity (BMI \geq 95 percentile) and children overweight with the following risk factors of insulin resistance, dyslipidemia, sleep apnea, central adiposity or family history of NAFLD/NASH.^{2,11} Screening younger patients is usually done on a case-by-case basis if multiple risk factors are present.²

Since there is a greater incidence of NAFLD in males vs. females androgens may not only worsen NASH, but estrogens could be a protective factor. Estrogen can lower the progression to

atherosclerosis with its anti-inflammatory effects of inhibiting lipid and cholesterol oxidation products. Halting this pathway impedes simple steatosis from developing into NASH. Androgen studies have demonstrated an increase in risk of NAFLD. Males not only have higher insulin resistance levels but also higher levels of triglycerides and lower HDL.⁶

It has been regularly confirmed that there is an ethnic disparity in the number of NAFLD cases, as there are more Mexican Americans than Caucasians affected. There are multifactorial reasons, perhaps due to increased visceral adiposity coupled with insulin resistance at equivalent BMI amongst the groups. These factors may further be influenced by socioeconomic status, diet, activity level and home location/accessibility. It is hard to pinpoint the exact cause that predisposes patients to fatty liver disease. Further studies are needed to elucidate genetic components and possible protective factors.⁶

Histologic differences help stratify the degree of severity of NAFLD. Simple fatty liver does not include hepatocellular injury. NASH and cirrhosis do include hepatocellular injury, both with and without fibrosis. This distinction helps physicians assist in directing treatment plans as weight loss (bariatric) surgery is not routinely indicated in pediatric medicine. Exceptions would include liver biopsy demonstrating advanced fibrosis consistent with NAFLD and the patient also exhibiting comorbidities.⁶

Advanced liver disease with cirrhosis presents with a constellation of physical exam findings: splenomegaly, hardened liver border, spider angiomas, palmar erythema, encephalopathy and jaundice.¹¹ Screening for NAFLD should be part of the evaluation of pediatric obesity-related conditions, such as T2DM, sleep apnea, early atherosclerotic heart disease and hypertension.²

For this patient, recommended lifestyle modifications could include increasing physical activity to 60 minutes every day, diet to include at least five servings of fruits and vegetables and are low in saturated fats, eliminating the consumption of sugar-sweetened beverages, less than two hours a day of screen time, weight loss and referral to a registered dietician. Sustainable weight loss is associated with improved cardiovascular risk and obesity-related comorbidities, such as NAFLD. Weight loss greater than 5% has been shown to have marked improvement in liver histology during adult studies. One pediatric study showed a 5 kg (11.02 lbs.) weight loss demonstrated improvement in NAFLD patient ALT and AST levels.¹⁰ Further studies are needed to determine the most-effective diet (low carbohydrate, low-glycemic index, low-fat diet, etc.)

Treatment goals are to repair the steatosis and inhibit fibrosis (and ultimately cirrhosis) and reduce the overall additional adiposity. Another aim of treatment places emphases on limiting risk factors that worsen NASH prognosis: obesity and T2DM. Treatment should concentrate on averting the two-hit process: limiting fatty liver infiltration (associated with insulin resistance and obesity) and reducing oxidative stress.¹⁴ Patients are encouraged to avoid alcohol, hepatotoxins and certain medications (valproate, acetaminophen, etc.) metabolized in the liver.¹⁴ Binge drinking can further potentiate the development of fibrosis.¹¹ Baseline labs in addition to possible biopsy, may be done

before initiating hepatotoxic medication. Further anticipatory guidance and counseling include discussing the risk of second-hand smoke exposure and discouraging adolescents against smoking and other nicotine delivery tools. Additionally, patients should be up to date with their vaccinations, especially hepatitis A and B.¹¹ As briefly alluded to in the clinical vignette, assessing psychosocial issues with appropriate and timely screening is imperative.¹¹ Addressing any underlying depression is part of the treatment plan as well.¹¹ This patient had an elevated PHQ-9 score, consistent with depression. Current literature suggests that pediatric patients with obesity lead to lower quality of life and risk of clinical depression.¹⁵ Bullying, poor self-esteem, social stigma, emotional eating and even discrimination are very real emotional ramifications of obesity.¹⁵

TREATMENT IN CHILDREN

Practice guidelines from the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) state that no currently available medications or supplements for NAFLD have evidence to support their use in children.¹¹ The AASLD identifies that metformin should not be used in children to specifically treat NASH or NAFLD. Only a few studies of vitamin E in children with biopsy-proven NASH are associated with limited if any benefit.^{16,17} However, the AASLD supports consideration of vitamin E in a dose of 800 IU/day for some children with biopsy-proven NASH, weighing risks and benefits since long-term safety is unknown.¹⁷

A follow-up visit is scheduled for six months to repeat fasting laboratory studies. Despite extensive counseling on diet and exercise by the clinician, the patient has been poorly compliant and has not made any drastic lifestyle changes. His BMI and blood pressure have remained the same. His repeated fasting lipid panel results, including ALT, AST, GGT and alkaline phosphatase, continue to remain elevated. What is the best approach to his risk for NAFLD?

Due to the elevated screening labs, further laboratory evaluation is needed to rule out other causes of liver disease, such as infection/hepatitis, celiac disease, hypothyroidism, genetic and autoimmune liver disease, etc. A liver biopsy can be considered to determine the degree of steatosis, inflammation and whether there is fibrosis present or lobular involvement.

The case for the use of ultrasound in the pediatric population, specifically Transient Elastography, has increased due to not only the growing number of pediatric NASH cases but the need for non-invasive diagnostic modalities to determine levels of liver fibrosis. The innovations of MR Elastography and Shear-Wave US Elastography have greatly improved the sensitivity, but there are still restrictions that make imaging difficult in the pediatric population. These limitations include breathing-induced tissue displacement, biologic tissue differences and variable disease distribution. Time-harmonic Elastography uses a steady, time-harmonic stimulus and helps obese patients because it can detect moderate fibrosis. The innovation of utilizing shear-wave detection

will help limit the use of invasive and recurrent procedures, such as frequent liver biopsies. Further studies are needed to investigate the accuracy of ultrasound in pediatric NASH patients to determine stages of fibrosis.^{18,19} These recommendations are similar to the adult population, as discussed later in this article.

Further imaging beyond ultrasound can include MRI-PDFF to quantify the degree of steatosis better.² The extent of histologic liver damage determines the natural history and prognosis. If simple steatosis, the clinical course is usually benign. However, if NASH is present, cirrhosis and related complications have an increased chance of developing. A liver transplant may be indicated if fibrosis progresses. The disease may even recur after transplantation.

Longitudinal studies are lacking regarding the presence of hepatocellular carcinoma in adults with previous childhood NAFLD. Preventing this potential, dire consequence is the impetus for consistent and diligent screening in at-risk pediatric groups (patients with obesity, insulin resistance or other aspects of metabolic syndrome). Weight loss and lifestyle changes are the mainstays of treatment, while multiple drug trials are pending. Sadly, with the staggering levels of pediatric patients with obesity, pediatric NAFLD and NASH are predicted to only increase. This community burden has dreadful public health consequences if not acted upon appropriately and with a sense of urgency. Perhaps this will shift the public health conversation to promote new policies surrounding school lunch options and activity within the family unit.⁸

CASE 2

A 45-year-old male presents to the family medicine clinic with concern for elevated blood sugars and alcohol use history. Last year, he was seen for a wellness physical and was diagnosed with insulin resistance with an initial Hga1c of 6.0%. During his physical last year, lifestyle changes, including weight loss and exercise, were recommended. One year later, he presents with a weight gain of 20 lbs. He currently smokes ½ pack per day for 15 years, drinks two beers daily and his parents both have T2DM. A physical exam includes BP 148/88 (confirmed on two occasions) and BMI 39 kg/m.2 He is taking no medications. New labs reflect a Hga1c of 7.8% with AST 80 U/L, ALT of 68 U/L, albumin of 4.0 g/dL and platelets of 170 109/L. His total cholesterol is 280 mg/dL, LDL is 160 mg/dL, HDL 35 mg/dL and TG 280 mg/dL. The rest of his metabolic panel is negative. His abdominal exam is consistent with enlarged pannus, non-tender, no masses, no obvious organomegaly.

Approaching this patient's health risks is multifactorial. He has new-onset T2DM, elevated blood pressure, liver enzymes and cholesterol. Cumulatively, this is metabolic syndrome.²⁰ (Table 3)

TABLE 3:

Criteria required for metabolic syndrome²⁰

CRITERIA (THREE OF FIVE REQUIRED)	INCLUSION RANGE
Waist measurement	35 inches or more for women or 40 inches or more for men
Triglyceride level	150 mg/dL or higher
HDL cholesterol level	Less than 50 mg/dL for women; less than 40 mg/dL for men
Blood pressure	130/85 mmHg or higher
Fasting blood sugar	100 mg/dL or higher

The patient presents with significant cardiovascular disease risk and possible NAFLD or even NASH. Further work-up is recommended and risk factor reduction is critical. It is important to consider that the pathogenesis of obesity, T2DM, NAFLD and CVD share many disease pathways. Evidence has also supported findings of increased chronic kidney disease in patients with NAFLD.¹³ It is well documented that NAFLD and NASH with cardiovascular disease increases overall mortality.¹³ Evidence also supports that metabolic syndrome promotes a faster progression of NASH to cirrhosis, leading to a liver transplant.¹³ Given this liver enzyme elevation and working diagnosis of NAFLD or possibly NASH, a comprehensive cardiac exam should be completed. Using the American College of Cardiology Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator²¹ that includes the patient's age, tobacco use, a new diagnosis of T2DM and lipid values, his 10-year risk is high at 32.2%. Recommendations to reduce this risk include blood pressure control (Table 4), weight loss (Table 5), lipid-lowering agents, blood sugar control and smoking cessation.²¹ The benefit of using statins in patients with NAFLD or NASH to reduce cardiac risk may outweigh the risk of the potential increases in liver enzyme levels. Blood sugar control for patients with NAFLD/ NASH currently includes pioglitazone. See Table 6 for medication discussions.

TABLE 4:

Blood pressure control recommendations, American Diabetes Association (ADA)²²

GRADE	RECOMMENDATION
C	For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk > 15%), a blood pressure target of < 130/80 mmHg may be appropriate if it can be safely attained.
A	Patients with confirmed office-based blood pressure \geq 140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals.
A	Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics or dihydropyridine calcium channel blockers).

A—Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered • B—Supportive evidence from well-conducted cohort studies • C—Supportive evidence from poorly controlled or uncontrolled studies • E—Expert consensus or clinical experience

Some patients with normal liver enzymes have been diagnosed with NAFLD.⁷ Given this patient's elevated AST, ALT and diagnosis of metabolic syndrome; he is at increased risk for NASH and fibrosis. According to the American Diabetes Association, grade C recommendation, determining the extent of his liver disease is the next step. Non-invasive testing measures for this patient are considered first, which include both imaging and biomarkers. Many of these non-invasive tests can be ordered by the primary care physician. These non-invasive methods have increased accuracy and can be used to rule out advanced disease. Consulting with a hepatologist and endocrinologist may help with test interpretation and disease staging.⁴

According to a systematic review by Leoni *et al.* of five international guidelines, including the American Association for the Study of Liver Diseases (AASLD), imaging recommendations include a consensus for using abdominal ultrasound as a first-line approach. Ultrasound can identify steatosis as mild, moderate and severe. Pooled sensitivities and specificities to distinguish moderate to severe fatty liver from the absence of steatosis has been reported for ultrasound at 85% (80–89%) and 93% (87%–97%), respectively.¹² However, the accuracy of ultrasound to diagnose steatosis in patients with a BMI > 40 is reduced.⁷ Transient Elastography (TE) is the technique of choice that uses both ultrasound and low-frequency elastic waves to quantify liver fibrosis (88–89% accuracy). TE produces a liver stiffness measurement (LSM). Imaging can also be performed with magnetic resonance elastography (MRE), however, this increases the cost and is most often used in clinical trials. Several studies are underway in efforts to replace liver biopsy with this non-invasive imaging measurements.¹²

Non-invasive biomarkers can be used for fibrosis prediction and risk stratification. The most suggestive markers in this patient include the elevated AST and ALT. Other common markers in NAFLD include elevated serum ferritin and low titers of autoimmune disease antibodies.⁷ Several of these biomarkers have been incorporated into predictive models; however, many have not been validated.¹² Two fibrosis scoring methods that have been clinically validated include the FIB-4 and NAFLD Fibrosis Score (NFS), which also predict cardiovascular risk with high sensitivity and specificity. Overall, for these two scoring methods, reported positive predictive values of 80% and negative predictive values of 90% had been confirmed.^{4,7,12} The FIB-4 score uses age, AST, ALT and platelets and the NFS uses age, BMI, IFG and diabetes, AST to ALT ratio, platelets and albumin. A FIB-4 score of < 1.3 or an NFS score of < -1.455 would suggest a low risk of advanced fibrosis. This patient's FIB-4 score is 2.57 and NFS score of 1.10 (correlates to F3-F4 fibrosis level). His higher FIB-4 or NFS scores predict intermediate-risk or higher and TE imaging is recommended. An intermediate or high risk of fibrosis determined by TE is considered an LSM of \geq 8KPa and a liver biopsy should be considered for confirmation.¹² Studies that combine the FIB-4 or NFS with TE have reported increased diagnostic accuracy.^{7,12} Several guidelines agree that liver biopsy should be performed if the diagnosis is uncertain or when NAFLD-related advanced (intermediate-high risk) disease is suspected by scoring or imaging.²³ If the scores are low, testing should be repeated every two years.⁷ Patients with NASH or fibrosis should be screened annually. Although the

AASLD does not provide an algorithm for diagnosis or follow up strategies for advanced fibrosis, they do support the strength of evidence of these non-invasive testing methods that are regularly used by the other guidelines.⁷

TABLE 5:

Nutritional recommendations for both NAFLD, NASH and T2DM are similar.^{7,9}

Reduction in caloric intake	A diet of 1200-1600 kcal/d, low fat (less than 10% saturated fat) and low carbohydrate (< 50% of total kcal) foods. The Mediterranean diet (plant-based, high in antioxidants and anti-inflammatory) is most commonly discussed among experts. Avoiding crash diets, limiting excess alcohol consumption (<40 g/d) and at least 7-10% weight loss is recommended.
Exercise	Aerobic and resistance training > 150 minutes per week.
Supplements	Vitamin E at 800 IU/d has been shown to decrease liver enzymes and histological inflammation improvement.; however, long term safety data shows conflicting evidence. See Table 6 for further discussion.
Bariatric surgery	Patients who are unresponsive to lifestyle changes and pharmacotherapy. Surgery has been shown to improve steatosis but is not unanimously recommended among all five of the systematic review guidelines.

The AASLD suggests that management of NAFLD focus on the common comorbidities of obesity, hyperlipidemia and T2DM. There are no FDA-approved medications specific to NAFLD currently marketed in the U.S. The AASLD recommends limiting drug therapy focused on the liver disease to only those with biopsy-proven NASH and fibrosis.¹⁷

INSULIN SENSITIZERS

Insulin resistance is a common finding in patients with NASH. Pioglitazone is a PPAR- γ receptor agonist and is the most-studied thiazolidinedione for NAFLD. Studies of pioglitazone 30 mg per day demonstrated improved aminotransferases as well as histologic findings of NASH. The most common adverse event associated with pioglitazone is weight gain, ranging from approximately 2.5 to 5 kg in clinical trials. Pioglitazone is associated with decreased bone density with long term use. Data are conflicting with regard to an increased risk of bladder cancer. Overall, the AASLD supports the use of pioglitazone in adults with biopsy-proven NASH with or without T2DM.¹⁷ Other antidiabetic agents have been evaluated for NASH. GLP-1 receptor agonists, such as liraglutide, show promise in initial trials evaluating the resolution of NASH.²⁴ The most recent guidance from AASLD suggests it is too early to consider treating liver disease with these agents. Metformin, however, has not been shown to be beneficial for NASH and is not recommended for this use by the AASLD.¹⁷

VITAMIN E

The antioxidant properties of vitamin E have generated interest in its use for NASH. The clinical trials of vitamin E typically included patients without diabetes and vary widely in the formulation and dosing of vitamin E, duration of treatment and concomitant lifestyle changes. General findings of the studies associate it with decreased aminotransferases and improvement in steatosis and inflammation.^{16,17} The AASLD recommends considering a dose of 800 IU per day for adults with biopsy-proven NASH who do not have diabetes.¹⁷ Importantly, the AASLD recommends against the use of vitamin E in patients with NAFLD without liver biopsy, NASH cirrhosis or cryptogenic cirrhosis, as it has not been adequately studied in these populations. It is also recommended to weigh the potential for increased bleeding risk and prostate cancer in individualized treatment decisions.^{16,17}

OTHER THERAPIES

Lipid-lowering therapy is an important modifier of cardiovascular risk in patients with NAFLD. While statin medications such as atorvastatin have demonstrated variable results in improving aminotransferases in this population, they continue to be an important option for treating hyperlipidemia in patients with NAFLD or NASH. The AASLD suggests avoiding treatment in those with decompensated cirrhosis.¹⁷

Studies of omega-3 fatty acids do not show consistent benefit for liver disease associated with NAFLD or NASH. However, the AASLD suggests continued use of omega-3 fatty acids for treatment of hypertriglyceridemia in patients with NAFLD.¹⁷

Although ursodeoxycholic acid (ursodiol) has been studied to improve hepatic parameters in NAFLD and NASH, data are conflicting and represent small trials with a varied endpoint. The AASLD recommends against its use.¹⁷

EMERGING THERAPIES

There is a great need for expanded pharmacotherapy options for NASH. Drug molecules that target modulators of hepatic inflammation, fibrosis, energy metabolism, fatty acid synthesis and the gut microbiome are under investigation and in various development phases.²⁵ Obeticholic acid and elafibranor are examples of agents further in the pipeline. Obeticholic acid is a farnesoid X receptor agonist currently under investigation for use in NAFLD. It is FDA-approved for primary biliary cholangitis who have an inadequate response to ursodiol. Younossi and colleagues²⁶ recently published findings from an interim analysis of a dose ranging placebo-controlled study of obeticholic acid in over 900 adults with NASH (stage F2-F3 fibrosis). The 25 mg daily dose showed significant improvement in fibrosis and the study is ongoing. Adverse events included pruritis and elevations in LDL cholesterol. The AASLD does not recommend off-label use of this agent currently, pending findings and analysis of the clinical outcomes once the trial is complete.¹⁷ Multiple insulin sensitizing agents are under clinical investigation for NASH and fibrosis. A placebo-controlled dose-ranging study of elafibranor, a dual PPAR

α - δ receptor agonist, demonstrated a trend towards improved NASH without fibrosis worsening.²⁷ Further trials are ongoing to determine its potential place in therapy.

TABLE 6:

Medication recommendations for adults with NASH^a

DRUG THERAPY ^b	CONSIDERATIONS
Pioglitazone	Consider use in biopsy-proven NASH in patients with or without diabetes
Metformin	Not recommended for this indication
GLP-1 agonists	Currently under investigation; insufficient evidence for clear guidance at this time
Vitamin E	Consider use in biopsy-proven NASH in patients without diabetes
Ursodeoxycholic acid	Not recommended
Statins	Supported for treatment of hyperlipidemia in patients with NAFLD/NASH unless decompensated cirrhosis/acute liver failure
Omega-3 Fatty Acids	Supported for treatment of hypertriglyceridemia in patients with NAFLD

^aRecommendations from the American Association for the Study of Liver Diseases¹⁷

^bNo drug therapies are currently approved for this indication by the U.S. Food and Drug Administration

GUT MICROBIOME

There is an emerging pool of studies evaluating gut microbiota and liver disease. Metabolic diseases have been linked to diet induced imbalance of the gut, also known as “leaky gut.”²⁸ Increased intestinal permeability or leaky gut is common in patients with NAFLD, which allows a larger amount of bacteria-derived products to enter the portal circulation.²⁹ This enhances the amount of damage incurred by the liver, which hastens the conversion from healthy tissue to the fibrotic tissue seen in NASH.²⁹ This has led to the development of what many are calling the gut-liver axis, which recognizes the direct connection the liver has to the gut via the portal system.²⁸ The microbiota of the gut changes in composition with diet; therefore, the liver is exposed to different compounds produced by the microbiota based on their presence or absence in the gut.²⁹ As a result, one potential solution for combating metabolic diseases, such as NASH, caused by the disruption of the gut-liver axis includes synbiotic supplementation.²³

Synbiotic supplementation includes the categories of probiotics and prebiotics.²³ Probiotics are microorganisms that confer beneficial effects on the host, while prebiotics are non-digestible carbohydrates that act as a nutrient source for favorable microorganisms in the colon.²³ One study by Ferolla *et al.* has shown promising results in using synbiotic supplements to modulate the gut flora. In this study comprised of 50 test subjects

27 with NASH and 23 without NASH, it was found that synbiotic supplementation with lifestyle changes is superior to lifestyle changes alone on the variables of BMI, waist circumference and body weight.²³ Steatosis, on the other hand, only showed attenuation with synbiotic supplementation.²³ The small sample size and differences in the experimental and control groups likely interfered with how robust this study's results were.²³ Given this information, the study by Ferolla *et al.* still showed promising results that should be explored further.

Synbiotic supplementation could be beneficial for NASH patients, given its effects on BMI, waist circumference and body weight, in that lowering these parameters could slow disease progression.²³ Also, synbiotic supplementation may be a solution that brings back the beneficial gut bacteria, allowing reestablishment of the gut-liver axis. There may still be a “leaky gut” due to previously damaged liver tissue, but the gut microbiota would no longer contribute to that damage, which may allow the liver the time it needs to heal itself. The question that remains is, which sets of bacteria would provide the best results? With further experimentation and more robust studies, synbiotic supplementation could prove to be an easily accessible solution for NASH patients.

CONCLUSION

One of the goals of this article was to highlight the epidemic of obesity in both the adult and pediatric populations and nonalcoholic steatohepatitis and the complications of the disease. The research brings consideration to a topic that does not receive a lot of attention in primary care and can help direct the approach to screening and treatment. As there is no clear consensus, even amongst academic societies, clinicians can use the data to determine their patients' course of action. This article seeks to provide information to modify current practices by utilizing emerging data. Primary care physicians should be cognizant of the signs of nonalcoholic steatohepatitis, incorporate cost-effective and judicious screening tests and encourage lifestyle modifications. The emerging literature surrounding the gut microbiome and medications encourages further research. Longitudinal studies are lacking but would provide helpful information regarding future implications of the disease process.

TABLE 7:

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ADA	American Diabetes Association
ALT	Alanine Aminotransferase
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
CT	Computerized Tomography
FDA	U.S. Food and Drug Administration
FIB-4	Fibrosis 4 Score
GGT	Gamma Glutamyl Transferase
GGTP	Gamma Glutamyl Transpeptidase
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
HgbA1c	Hemoglobin A1c
IU	International Units
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LSM	Liver Stiffness Measurement
MRE	Magnetic Resonance Elastography
MRI-PDFF	Magnetic Resonance Imaging Proton Density Fat Fraction
NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
NASPGHAN	North American Society of Pediatric Gastroenterology, Hepatology and Nutrition
NFS	NAFLD Fibrosis Score
Non-HDL-C	Non-High Density Lipoprotein Cholesterol
PHQ-9	Patient Health Questionnaire 9
T2DM	Type 2 Diabetes Mellitus
TE	Transient Elastography
TG	Triglycerides

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BRIEF REPORT

RAPID DEVELOPMENT AND DEPLOYMENT OF RESPIRATORY EVALUATION CLINICS IN RESPONSE TO THE COVID-19 PANDEMIC TO KEEP STAFF AND PATIENTS SAFE

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KEYWORDS:

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COVID-19 Testing

Family Medicine

SARS-CoV-2

ABSTRACT:

The world as we knew it changed at the beginning of 2020 with the explosion of the global pandemic caused by SARS-CoV-2, a.k.a. COVID-19. As of January 10, 2021, the novel coronavirus has infected over 89 million people worldwide and killed over 1.9 million. In the U.S., there have been 22 million people infected and 373,000 deaths. It has never been more important to protect our vulnerable patients and staff from infectious disease, especially during the time they spend in our offices and clinics. It quickly became apparent that there was a need for a dedicated location where patients could be seen that were too ill to be evaluated via telemedicine, but not ill enough to be sent to the Emergency Department (ED). To fill this need, our primary care network developed the Respiratory Evaluation Clinic (REC) concept. These were two geographical locations where the outlying clinics could send potentially infectious patients to evaluate and test COVID-19. Some recommendations, adaptations, lessons learned and the REC clinics' expansions to other locations throughout our network are discussed.

INTRODUCTION

The world as we knew it changed at the beginning of 2020 with the explosion of the global pandemic caused by SARS-CoV-2, a.k.a. COVID-19. As of January 10, 2021, the novel coronavirus has infected over 89 million people worldwide and killed over 1.9 million. In the U.S., there have been 22 million people infected and 373,000 deaths.¹

It has never been more important to protect our vulnerable patients and staff from infections, especially during the time they spend in our offices and clinics. At the beginning of this pandemic, there was a great deal of focus on procedures and protocols to protect staff and patients in the hospital setting, especially as hospital Emergency Department (ED) were overwhelmed in some areas.²

As clinic access to patients became restricted, there was an immediate shift to telemedicine. Virtual visits increased exponentially for most outpatient care providers. It quickly became apparent that there was a need for a location where

patients could be seen that were too ill to be evaluated via telemedicine but not ill enough to send to the ED.

When evaluating the outpatient medical centers' infectious disease practices, it became very clear that we needed improved precautions to protect the staff and our vulnerable patients from this highly infectious disease. These precautions included staff selection and training using a team-based approach, adaptation of workflow to decrease the likelihood of cross-contamination, coordination with the laboratory and clinic administration to ensure availability of proper testing supplies and personal protection equipment. There was also a great need to conserve Personal Protective Equipment (PPE) such as N95 masks, gowns, face shields and other resources such as testing kits and cleaning supplies early on during the pandemic in the U.S.

Our department has 30 satellite outpatient clinics spread over five counties and two states. These clinics range in size from solo physician practices to large medical centers. The patient population in the clinics varies from those who live in affluent coastal communities to some of Northeast Florida's most at-risk patients in Jacksonville's urban core. It was important to design a relatively easy system for patients to access regardless of the demographics.

Most physician offices were not prepared to safely have patients with a potential active infection come to the clinic for evaluation. To fill this need, our team developed a Respiratory Evaluation Clinic (REC). These were two geographical locations with specific

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protocols in place to evaluate patients with potentially infectious diseases. The outlying clinics were able to send suspect patients to the RECs for evaluation and testing for COVID-19. These protocols were later expanded to additional clinics so they could safely perform testing for their patients.

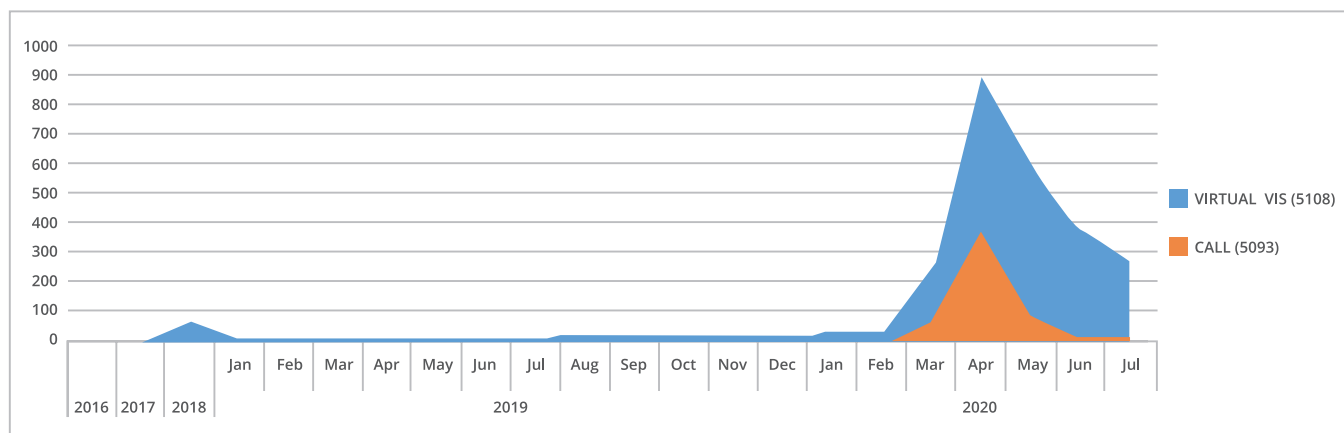
SHIFT TO TELEMEDICINE

For both patient and provider safety and comfort, there has been a significant shift across the nation to providing care through telemedicine due to COVID-19.³ Telemedicine is a useful tool in primary care to provide convenient care for patients using live synchronous video, ideally through a HIPAA secure platform. A wide variety of conditions can be managed easily via telemedicine, including upper respiratory infections, mental health conditions, simple urinary tract infections, etc. In Florida, patients on non-opiate controlled substances who are presenting for refills can be seen via telemedicine. During the COVID-19 pandemic, established patients who take chronic opiates for a chronic condition can also be seen via telemedicine.⁴ There are times when a provider may see a patient via telemedicine and decide that an in-person evaluation may be needed, for example, to perform a cardiorespiratory examination. Before the pandemic, these patients were seen in the clinic within 24 hours of their virtual visit. During the pandemic, patients needing additional in-person evaluation are directed to the REC. For clinics designated as a REC, telemedicine offers the ability to evaluate patients' history and need for COVID-19 testing while minimizing clinic staff and other patients' exposure time.

Before COVID-19, our institution utilized another application of telemedicine by performing a virtual hospital consult service. This allowed primary care providers to connect via telemedicine with their patients hospitalized at our institution. This virtual check-in provides a smoother transition of care as patients are discharged home. Since COVID-19, this service is even more important as hospitals are limiting in-person visitors and have been expanded to allow family members to do virtual "check-ins" with their loved ones.

FIGURE 1.

Total of visits utilizing telemedicine conducted in the family medicine department, 2016–2020



To have a telemedicine visit at our organization, where EPIC is the electronic medical record system used, patients must have:

- 1) An account set up for the patient portal, which is called "MyChart®."
- 2) Access to a telemedicine capable device such as a smartphone, tablet or computer.
- 3) Access to Zoom on that device.

Our visits are carried out on a HIPAA compliant version of Zoom, with the meeting link sent to patients through their MyChart® account. During the COVID-19 pandemic, our organization has liberalized the technical requirements for patients, allowing those who have access only to Zoom but not MyChart® to participate in telemedicine visits. Patients are sent a link directly allowing those with non-telemedicine capable devices to have telemedicine visits utilizing the Doximity Dialer that allows non-smartphone users to have a telemedicine visit.⁵

Adopting telemedicine across our department and organization before COVID-19 was slow due to provider hesitation to embrace technology and/or concern about limited physical exam capability via telemedicine and due to lack of parity laws in Florida for telemedicine visits. From the time that the telemedicine program first started in the family medicine department in 2016 until March of 2020, it conducted a total of 3,383 visits utilizing telemedicine (Figure 1). COVID-19 necessitated a paradigm shift in how medicine is practiced from traditional in-person clinic visits to telemedicine. Providers who were initially hesitant to use telemedicine were trained quickly to continue caring for patients. Additionally, since COVID-19 first broke, virtually all payors have allowed telemedicine visits to be paid on par with in-person visits. The U.S. Centers for Medicare and Medicaid Services have also allowed payment for telephone calls that are well documented and based on time.⁶ Between March 1, 2020 and July 24, 2020, our institution's family medicine department conducted a total of 26,044 telemedicine visits.

DEVELOPING A RESPIRATORY EVALUATION CLINIC

Cluster concept

In clinic systems where several facilities spread out throughout a wide geographical area, using a cluster concept of care can improve patients' access and availability. The cluster concept refers to having geographically located "sister clinics" that can care for patients from nearby clinics in case of emergency closures or disaster. Our system has used this approach during hurricanes, power outages and most recently when one clinic closed because several caregivers in the facility tested positive for COVID-19.

The cluster clinics are set up proactively by having insurance agreements in place so that care provided by sister clinics are properly reimbursed, that call centers are aware of the potential shift in the location of care for the patients and that advanced practitioner protocols are in place so that these providers can be supervised remotely from another location. Care can be routed to the sister clinic for evaluation and treatment in case of the emergency closure of a facility or for clinics that are not prepared to evaluate potentially infectious patients.

Team selection

Developing a timely, aggressive and collaborative strategy to care for our moderately ill patients and staff, while protecting our medical team, required input from administration, hospital infection control and microbiology, laboratory medicine, nurse educators, purchasing and providers. Using the Centers for Disease Control and Prevention (CDC) resources as our guide, equipment, staff selection, training and workflows were established with a team-based approach, which provided safeguards from cross-contamination, reliable test results and expeditious care.⁷

The team should be all volunteers if possible, especially for those who are providing direct patient care. Those personnel should also be vaccinated for COVID-19 before starting to provide care to potentially infectious patients. Choosing an inclusive team is instrumental in the setup and workflow of the clinic.

The front staff helps maintain the patient schedule, assist the patient with the virtual visit technology, collect copays and provide patient instructions about the upcoming visit. The MAs provide supportive patient care, coordinate patient flow and handle test processing. They ensure the rooms are cleaned and sanitized to health care standards between patient visits. The back-office lead coordinates MAs and is the on-site problem solver. The office manager/administrator coordinates providers' schedules, manages equipment supply, notifies the call center of the availability of the REC clinic and assists with billing and facility adaptation. In addition to direct patient care, the providers should remain current with ever-changing updates and guidelines for evaluating and treating COVID-19 patients. This includes the use and limitations of antibody testing as it becomes available.

Periodic team meetings to assess the problems as they arise, address the availability of PPE and testing supplies and evaluate and adapt work flow are recommended. These meetings should include members of the rest of the clinic to discuss any positive or

negative effects the REC has on the rest of the clinic operations. During this emotionally charged time, the staff may have an increased stress level both at work and at home. Some of the staff felt more reassured that their potential infectious risk at work was decreased because of the safety precautions that were put in place.

Workflow

Providers, staff and the call center are made aware of the availability of the REC through emails, video and zoom meetings by our institutional leadership. Patients that call for an appointment are pre-screened by the office staff or the call center for symptoms of, or exposure to, COVID-19. Those that are considered to need an evaluation are scheduled for a telemedicine visit with either a physician or advanced practice provider (APP). Patients that have mild symptoms are recommended to stay home and given instructions for home care, self-isolation and advised of warning signs that may escalate their need for in-person care. Those patients with severe symptoms, including progressive worsening of shortness of breath, chest pain, dyspnea or unremitting cough, are directed to the ED and advised to wear a mask.

The need for a face-to-face visit is determined clinically with a low threshold for those over 65 or with an underlying health condition such as COPD, diabetes, heart failure, active cancer or recent hospitalization for cardiovascular disease. Patients with moderate symptoms, especially with exposure to COVID-19, such as shortness of breath, fever or dry cough, are scheduled to be evaluated in the REC clinic.

Staff members responsible for screening the patients are located outside the facility or at the entry. Symptomatic patients at risk because of age and coexisting conditions may be considered for Bamlanivimab therapy. Well patients and REC patients use a separate entry and hallway if possible. Well patients screened at the entry who have a temperature of greater than 100.4°F, are directed to the REC clinic. Some REC patients can be fully evaluated in their vehicle. Those who need more extensive evaluation such as EKG and pulse oximetry reading should be evaluated inside the clinic. While the REC is established for evaluating COVID-19 patients, it is important to remember that patients with Coronavirus symptoms may have additional disease states, including asthma, COPD exacerbation, angina, pneumonia or bronchitis.

REC patients are asked to wear a mask and stay in their vehicle and notify the staff of their arrival. Patients without a vehicle should remain outside or in areas designated for potentially infected patients. They should maintain a minimum of social distancing at least six feet from any other person. These patients are not seated in the waiting room and are brought immediately into a designated exam room by MA or nurse in PPE. Some of the patient's history can be gathered via telephone, while the patient is in the vehicle or exam room, to limit the time of direct exposure to others.

All equipment needed, including stethoscopes or pulse oximetry instruments, are prepped by wiping down with an approved cleaning solution and placed at the door or in the exam room

along with the testing equipment. Having donned PPE, the provider enters the room and evaluates the patient and leaves all equipment and supplies in the room. At the completion of the visit, the PPE is doffed by the provider using the doff protocol. The MA or nurse in PPE then escorts the patient out of the clinic. The testing equipment is collected and the room is then sanitized and the MA or nurse wipes down all surfaces and equipment. Results of tests, including COVID-19, are communicated to the patient and their primary care provider via the electronic portal or telephone. Some patients who are more ill may require future telemedicine or in-person visit for follow up.

After successfully implementing the REC concept at the two initial clinics, the model was duplicated at several of our other outlying clinics. The lessons learned by developing and implementing the REC was presented to the new clinics. We conducted a team-based educational sessions involving the office leadership and staff, to tailor the concepts to the clinic's personnel and individual clinic layout.

Donning and doffing

The concept of don and doff refers to the sequence for putting on and how to remove PPE safely. This is a very important work practice to master to protect oneself and limit the spread of contamination. There are several types of PPE based on the level of precaution and the doffing and donning should be tailored to the specific type of PPE. The CDC requires strict adherence to standard, airborne and contact precautions, plus eye protection for the care of patients with or under investigation for COVID-19.⁸

The ideal necessary PPE required for the appropriate care of patients with or under investigation for COVID-19 includes:

1. Isolation gown
2. Fit tested N95 mask
3. Face shield or goggles for eye protection
4. Gloves

The donning of PPE should take place in a safe, decontaminated area. All PPE items are ideally placed in one area outside the patient room. When entering the patient room provider should don all PPE. The donning sequence includes: Perform hand hygiene, don gown, don mask, don face shield or goggles, perform hand hygiene and don gloves. Some providers may elect to double glove.

The doffing of PPE is critical in preventing contamination of clothing, skin or mucous membranes with potentially infectious material. It is important to perform hand hygiene between doffing steps. The doffing begins at the exit of the patient room and should not be in the donning area. Sequence for doffing includes: Perform hand hygiene over gloves, doff gown and doff gloves if double gloves, hand hygiene over gloves. If wearing single gloves, doff gloves, perform hand hygiene, then don clean gloves. Use a disinfectant wipe to clean the face shield or goggles' surface, remove face shield, disinfect face shield, perform hand hygiene on gloves, remove the mask, remove gloves and perform hand hygiene. Other CDC recommendations to protect and limit the

spread of contamination include keep hands away from the face, limit surfaces touched, change gloves when torn or heavily contaminated and perform frequent hand hygiene.

CONCLUSION

The COVID-19 pandemic has impacted millions of people from all walks of life worldwide. The response from the medical community at all levels was remarkably swift. It brought generational changes in medical practices, especially our approach to treat potentially infectious patients. Telemedicine quickly became a preferred and safe option for many patients and providers. The expansion of telemedicine will certainly carry forward even when this pandemic is better controlled. The innovation and development of the REC was an essential service offered to provide safe medical care to well and ill patients. For an REC to be successful, collaboration and buy-in from all stakeholders are vital and the location should be in an optimal geographic location. The team should be a volunteer and help identify the safest area in the clinic for patient evaluation and testing. Huddles and team meetings help keep communications open and provide emotional support, to maintain a strong and confident team in their ability to deliver health care during these unprecedented times. The lessons learned, and the adaptations we have undergone, will shape the future of medicine for years to come and will ensure that we will be much better prepared for the next challenge that is sure to come.

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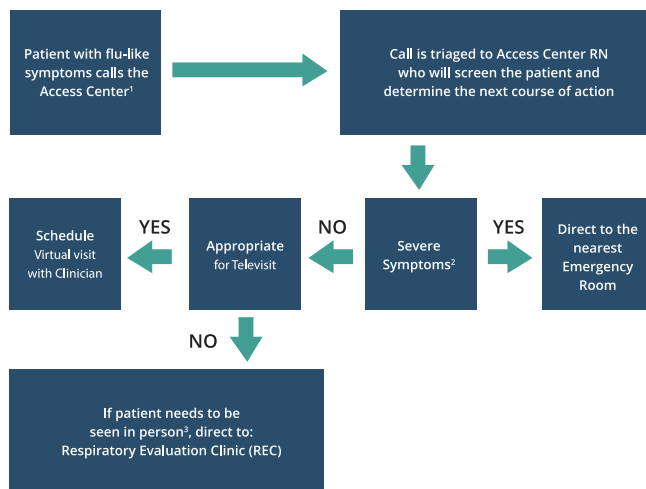
TABLE 1.

REC clinic recommendation

TEAM SELECTION
<ul style="list-style-type: none"> • Team members should be all volunteer. • From the beginning involve key personnel: front staff, MA's, back office lead, office manager and administrator.
VACCINATION
<ul style="list-style-type: none"> • All team members should be vaccinated for Covid-19 before beginning work in the REC.
CLARIFY MISSION/ CRITERIA FOR PATIENT SELECTION
<ul style="list-style-type: none"> • Patients suspected of Covid-19 with moderate symptoms. • Ill patients needing an in person visit. • Patients under investigation for Covid-19, especially those at high risk. • The preferred evaluation for mildly ill patients is telemedicine. • Patients with severe symptoms or red flag symptoms such as worsening shortness of breath, chest pain are directed to ED. • Well patients screened at the entry and found to have a temperature greater than 100.4 F.
NOTIFICATION
<ul style="list-style-type: none"> • Inform referral sources of the availability of the REC. • Include the call center staff members and providers.
CLUSTER CONCEPT
<ul style="list-style-type: none"> • Have agreements in place between clinics for APPs and insurance coverage so patients can be seen and insurance can be billed at various primary care locations in the network.
LOCATION/FACILITY
<ul style="list-style-type: none"> • Make sure to have a specific area away from well patients for evaluation, entry and exit. • Consider designated parking areas just outside the exit. • Staff and well patients will enter the main lobby and be tested for temperature. No touch thermometer preferable. • REC patients will be evaluated in the car or directed to the REC exam rooms without stopping in the waiting room or lobby.
DOFFING AND DONNING
<ul style="list-style-type: none"> • Have an assigned area that is recognized by all staff. • Have a posted list of correct order for doff and donn.
EXAM ROOMS
<ul style="list-style-type: none"> • Have at least two exam rooms dedicated for potentially infected patients. • Consider testing outside, weather and other conditions permitting.
SUPPLIES
<ul style="list-style-type: none"> • Have adequate PPE and tests kits/swabs. • Do daily or weekly inventory.
WIPE DOWN AND SANITATION
<ul style="list-style-type: none"> • Have a wipe down schedule and protocol.

TABLE 2.

Algorithm for patients with flu-like symptoms



1. Lower respiratory tract-like flu symptoms typically include some combination of fever, new cough, myalgia, and shortness of breath, isolated sore throat, nasal congestion, sneezing and sinus congestion typically represent URI rather than LRI symptoms. Anosmia may point to COVID-19.
2. Severe symptoms are judged clinically, but include severe cough, shortness of breath or, for patients over 65, a temperature greater than 100.4F°.
3. Need for face-to-face visits when patients are older than 65; have co-morbid conditions such as COPD requiring treatment, diabetes, heart failure, or active cancer; are immunosuppressed; or had a hospitalization due to cardiovascular disease in the past year.

Unscheduled Walk-in Patient with Flu-like symptoms

1. Provide patient (and family) with surgical mask.
2. Politely ask patient to back to their car or wait outside.
3. A clinical person will call or meet the patient and follow the above algorithm as it pertains to Televisit or in-person visit.

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CLINICAL IMAGE

A RARE CAUSE OF DYSPNEA

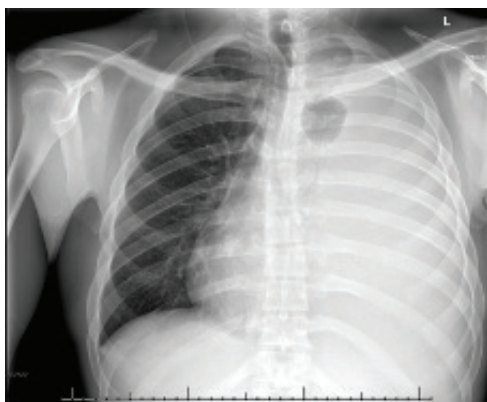
Vishesha Patel, DO, PGY1¹; David Lang, DO¹¹ Beaumont Farmington Hills, Farmington Hills, MI

INTRODUCTION

A 38-year-old male with a past medical history of necrotizing pancreatitis and splenic vein thrombosis, diagnosed six months prior, presents to the emergency department with a chief complaint of dyspnea of three days duration. The patient experienced sudden onset difficulty breathing while working on his truck at home, with associated palpitations, both resolving after giving minutes of rest. After three days, the patient reported mild improvement in his dyspnea after using his significant others albuterol breathing treatment. However, due to persistent discomfort, the patient reported to the emergency department, where he underwent a chest x-ray and computed tomography (CT) of the chest with IV contrast. The patient denied any fevers or cough at home. The patient works part-time on the weekends at a turkey processing farm, with appropriate use of protective equipment, including barrier garments and a mask. He smokes six-seven cigarettes a day for the last ten years, admits to drinking alcohol occasionally and denies any other drug abuse, except for marijuana. The patient has a past medical history of liver cirrhosis secondary to alcohol abuse and surgical history of appendectomy. He denies any URI symptoms, chest pain, abdominal pain, nausea or vomiting, headaches or vision changes. He denies any history of travel and reports the only medication he takes is Motrin® for pain relief.

FIGURE 1:

The patient's chest x-ray.



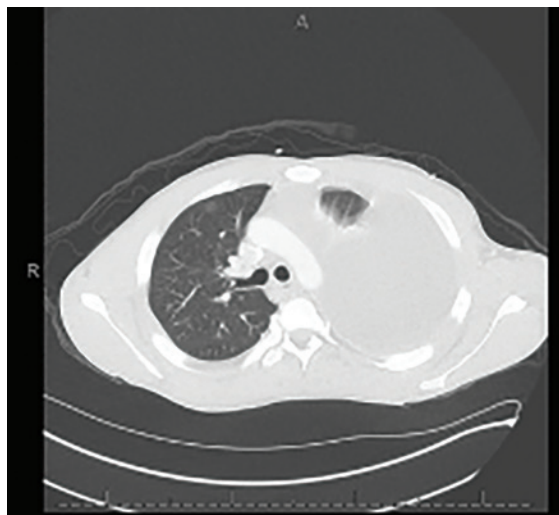
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FIGURE 2:

The patient's computed tomography (CT) of the chest with IV contrast.



QUESTIONS:

- Based on the patient's past medical history, clinical presentation and imaging, which of the following is the most likely underlying etiology for the pleural effusion?
 - Congestive heart failure
 - Pancreaticopleural fistula (PPF)
 - Pneumonia
 - Pulmonary embolism
- What is the best imaging study of choice for diagnosing this disease?
 - Endoscopic retrograde cholangiopancreatography (ERCP)
 - Magnetic resonance cholangiopancreatography (MRCP)
 - Lung biopsy
 - Computed tomography (CT) of chest-abdomen-pelvis
- What is the next best intervention to provide symptomatic relief for this patient's pleural effusion?
 - 40mg IV Lasix
 - Thoracentesis
 - CT guided lung biopsy
 - IV antibiotics

ANSWERS:

1. Based on the patient's past medical history, clinical presentation and imaging, which is the most likely underlying etiology for this patient's pleural effusion?

Correct answer:

B) *Pancreaticopleural fistula (PPF)*

PPF is a rare diagnosis that occurs in approximately 0.4% of patients with pancreatitis.¹ It is caused by chronic pancreatic inflammation in which pancreatic secretions drain directly into the pleural cavity through an abnormal connection between the pancreatic duct and the pleural space, causing an amylase-rich pleural effusion.¹ It usually requires a high index of suspicion as patients typically present with pulmonary symptoms such as dyspnea caused by the pleural effusion rather than abdominal symptoms caused by pancreatitis.¹ Other than resulting from a chronic inflammatory process, PPF can also occur from acute inflammation or traumatic or iatrogenic rupture of the pancreatic duct.¹ Congestive heart failure is a progressive disease in which the heart's function as a pump is inadequate to meet the body's needs. It is a less common finding in young individuals, especially with no prior cardiac history. CXR findings would be consistent with cardiomegaly, cephalization and Kerley lines. Pneumonia and pulmonary embolism can be common causes of acute dyspnea. Pneumonia could be a likely diagnosis in this patient with a history of exposure to birds; however, the rest of the clinical findings and imaging do not support this choice. Although a CXR would not be indicative for a PE, a CTPE was performed on this patient, revealing no blood clots in the pulmonary vasculature, making PPF the correct answer choice.

2. What is the best imaging study of choice for diagnosing this disease?

Correct Answer:

B) *Magnetic resonance cholangiopancreatography (MRCP)*

PPF is a rare complication of chronic pancreatitis consequent to disruption of the pancreatic duct. Although CT is the standard modality for evaluating acute pancreatitis and its complications, such as pseudocysts, it is not sensitive in assessing the anatomy and morphology of the fistulous tracts.² ERCP has emerged as both the diagnostic and therapeutic option in select patients with PPF; however, MRCP still remains the radiological investigation of choice as it not only helps in diagnosing the presence and site of the fistulous tract but also helps determine management options.³

3. What is the next best intervention to provide symptomatic relief for this patient's pleural effusion?

Correct answer:

B) *Thoracentesis*

Massive pleural effusion caused by PPF is a very rare complication of pancreatitis, most commonly associated with alcoholic chronic pancreatitis.² In cases of a PPF resulting in a hydrothorax, approximately 75% occur on the left side, although they may also be right-sided or bilateral.² Thoracentesis should be performed in patients with a pleural effusion. It not only helps with diagnosis by obtaining fluid for biochemistry, but it also alleviates pulmonary

symptoms such as dyspnea.² Pleural effusions associated with PPF are usually exudative in nature and although there is no cutoff level to establish a diagnosis, pleural amylase is usually >1000 U/L.⁴ CT guided lung biopsy would aid in diagnoses of malignancy related pleural effusion and also would not provide any type of symptomatic relief to this patient. While IV antibiotics and IV Lasix are potential adjunctive treatments, they would not provide immediate relief of the pulmonary symptoms this patient is experiencing.

DISCUSSION

Pancreaticopleural fistulas are a rare complication of acute or chronic pancreatitis and are most commonly associated with alcoholic pancreatitis.² They can also occur due to gallstone pancreatitis, idiopathic pancreatitis, trauma or pseudocysts. They occur in less than 1% of patients with acute pancreatitis, 0.4% of patients with chronic pancreatitis and 4.5% of patients with pseudocyst.¹ Chronic pancreatitis is a progressive and irreversible inflammatory process characterized by the transformation of pancreatic parenchyma into fibrotic tissue.⁵ Additionally, chronic alcohol consumption can cause acute focal inflammation of the pancreatic ducts and form protein plugs, which can subsequently cause temporary blockage of the small duct branches and lead to main pancreatic duct dilation.⁶ Due to this inflammation, an abnormal connection is known as a fistula, which sometimes forms between the pancreatic duct and the pleural space, causing pancreatic secretions to traverse into the pleura leading to a pleural effusion that is rich in amylase.⁵

The pathophysiology of PPF consists of ductal disruption on the posterior surface, which then results in the thoracic fluid collection as the fluid spreads retroperitoneally through pathways of least resistance at the aortic or esophageal hiatus.² For this reason, patients with PPF are more likely to present with pulmonary symptoms related to the pleural effusion rather than abdominal symptoms related to pancreatitis leading to a delay in diagnosis.⁷ Many patients may even undergo extensive lung investigation before the pancreas is identified as the dysfunction's primary organ. The diagnosis is usually performed by thoracentesis after a chest radiography, with laboratory findings of elevated amylase levels, generally above 1,000 U/L, although no diagnostic level has been recognized.⁷ Once the diagnosis has been established, imaging is used as an adjunct to characterize the anatomy and location of the fistulous tracts. Even though CT scan is the preferred choice for the evaluation of pancreatitis, for assessment of the fistulous tracts, MRCP is deemed superior.³ Additionally, ERCP was previously preferred due to it being diagnostic and therapeutic in nature; however, MRCP is non-invasive when compared to ERCP and it helps with visualizing the pancreatic duct beyond simple strictures, making it the current imaging modality of choice in patients with PPF.⁷

Regarding the treatment of PPF, no treatment modality has been deemed superior to others. PPF can be treated medically, endoscopically or surgically, based on individual patient presentation. Immediate thoracentesis with chest tube placement to drain the recurrent pleural effusion is often the first step and provides immediate relief of symptoms. Endoscopic treatment with ERCP stenting to the pancreatic duct has also been shown

to be successful, with the main goals of blocking the abnormal connection of the pancreatic duct with pleura as well as to keep the duct open for the pancreatic secretions to flow down the path of least resistance into the duodenum.¹ Obvious complication includes anatomical disruption of the duct and recurrent fluid accumulation. If and when medical and ERCP treatment fails, surgical treatment is the best resort. The main principle of surgical treatment is to form a pancreatic enteric connection to achieve adequate drainage of the pancreatic sections with or without pancreatic resection.¹ The most common surgery reported in the treatment of PPF is distal pancreatectomy with pancreaticojejunostomy.¹ King *et al.* reported a 94% success rate for surgical treatment compared to a 31% success rate for medical treatment.⁸ The same study also reported that medical treatment takes 50% more time than the time required for surgical recovery and that 70% of the reported surgical complications occurred in patients treated initially with medical management. Generally, the rule seems to be to treat normal or mildly dilated pancreatic duct with the trial of medical therapy, those with ductal disruptions or strictures to undergo endoscopy and reserve the surgical option for those with a complete ductal obstruction or if stenting is impossible based on image findings.⁹

CONCLUSION

Pancreatic pleural fistulas remain to be rare, however, they still present as a significant problem in patients with pancreatic disease. Dyspnea is a symptom that clinicians often encounter in their practice and many usually place cardiopulmonary etiology at the top of the differential.¹⁰ Nevertheless, it is always important to recognize the patient's history, rather than relying on their symptoms alone. The single most important diagnostic procedure is a pleural tap to determine the level of pleural fluid amylase.⁹ ERCP used to be the preferred investigative technique for confirming the diagnosis; however, MRCP is now deemed superior due to its noninvasive nature. For treatment, as always, deciding which route to proceed is different based on individual patient presentation and a thorough risk and benefit assessment needs to take place between the physician and the patient. Strict follow-up with primary care physicians to reduce complications such as PPF should be encouraged for pancreatic disease patients.

AUTHOR DISCLOSURES: No relevant financial affiliations or conflicts of interest. If the authors used any personal details or images of patients or research subjects, written permission or consent from the patient has been obtained. This work was not supported by any outside funding.

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PATIENT EDUCATION HANDOUT

Constipation: How OMT Can Help

Nida Jiwani, DO

Ronald Januchowski, DO, FACOFP, Editor • Paula Gregory, DO, MBA, CHCQM, FAIHQ, Health Literacy Editor

Constipation is a common problem that approximately 63 million Americans visit their physician for every year. Usual treatments for constipation include lifestyle changes, such as high fiber diets or the use of laxatives and enemas. However, osteopathic manipulative treatment (OMT) can also help with the symptoms of constipation.

Your osteopathic family physician has been trained in OMT, which takes into consideration your anatomy, lymphatic system and circulation to assess the cause of and then treat your constipation. OMT performed on the abdomen can improve blood and lymph circulation along with decongesting the intestines and improving smooth muscle tone.

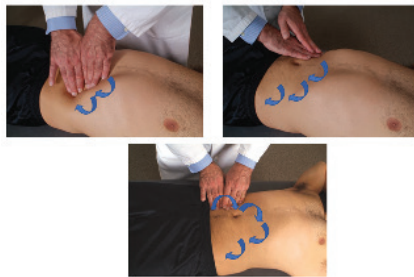
OMT TECHNIQUES TO TREAT CONSTIPATION

Colonic stimulation

The physician will apply pressure on your abdomen while you are lying down on your back in guided motions following your colon's pattern to stimulate your intestines. (Figure 1)

FIGURE 1:

OMT Colonic Stimulation



Sacral rock

The physician will use your breathing to exaggerate your sacrum's motion during inhalation and exhalation while you are lying down on your stomach to improve any restriction of the sacrum that may be causing your constipation.

MEDICAL CARE & TREATMENT OPTIONS

If you have any further questions about how OMT can help with constipation, please contact your osteopathic family physician. Your family doctor can help you determine which technique will be best for you and/or if you need additional sources of symptom relief. Contact your healthcare provider if your constipation is associated with blood on the toilet paper, fevers or weight loss. In case of any emergency, you should call your doctor or 911 right away.

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PATIENT EDUCATION HANDOUT

Substance-Induced Psychosis: Identifying Symptoms and Triggers

Fatima Zehra Siddiqui, MD, PGY-3; Michelle Taylor, MD, NBC-HWC

Ronald Januchowski, DO, FACFP, Editor • Paula Gregory, DO, MBA, CHCQM, FAIHQ, Health Literacy Editor

Substance-induced psychosis occurs due to exposure to a drug of abuse, medication or toxin. Symptoms can occur with intoxication or withdrawal of a drug. Symptoms will stop when exposure to the substance is discontinued.

SYMPTOMS

Major symptoms of psychosis are delusions and/or hallucinations. Delusions are fixed and false beliefs that are not in line with an individual's culture or character. Other symptoms include unclear thoughts, being upset and/or violent outbursts.

SUBSTANCES THAT MAY TRIGGER PSYCHOSIS

Drugs Of Abuse

- Alcohol
- "Bath salts" (MDPV/mephedrone)
- Cocaine
- Inhalants (i.e., toluene, butane, gasoline)
- Ketamine
- LSD
- Marijuana
- MDMA/Ecstasy
- Mescaline
- Methamphetamine
- Synthetic cannabinoids (i.e., "spice")
- PCP (phencyclidine)
- Psilocybin-containing mushrooms
- Salvia divinorum
- Synthetic "designer drugs"

Medications

- Abacavir
- Acyclovir
- Amantadine
- Amphetamines
- Anabolic steroids (i.e., testosterone, methyltestosterone)
- Atropine
- Barbiturates
- Benzodiazepines
- Bromocriptine
- Bupropion
- Chloroquine
- Corticosteroids (prednisone, dexamethasone, etc.)
- Dextromethorphan
- Digoxin
- Diphenhydramine
- Disopyramide
- Dronabinol
- Efavirenz
- Indomethacin
- Interferon alfa-2a/2b
- Levodopa
- Mefloquine
- Meperidine
- Methylphenidate
- Nevirapine
- Pentazocine
- Pramipexole
- Propafenone
- Quinidine
- Scopolamine
- Selegiline
- Zonisamide

Toxins

- Carbon monoxide
- Organophosphates
- Heavy metals (arsenic, manganese, mercury, thallium)

TREATMENT

If you or a family member are having concerning symptoms, please call your doctor immediately or go to the nearest emergency room. Treatment is based on the particular medication, drug of abuse or toxin.

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- COVID-19: Management of the obstetrics patient with osteopathic component
- COVID-19: Management of the pediatric patient including neonates with COVID-19 positive mothers with osteopathic component
- COVID-19: Management of the special needs patient with osteopathic component
- COVID-19: Remote consultations: A guide to assessing patients by video or voice call with osteopathic component
- COVID-19: New office procedures for safety with osteopathic component
- COVID-19: Communication aids: How to talk to patients about difficult topics related to COVID-19 with osteopathic component
- Assessing and managing the adult patient with asthma during COVID-19 pandemic
- Lupus review with osteopathic component
- Osteopathic considerations in pain management
- Polypharmacy in the elderly



Phy-si-cian

/fə'ziSHən/

Noun

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